(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 112142855 A
(43)申请公布日 2020.12.29

(21)申请号 202011051789.5

(22)申请日 2013.05.17

(66)本国优先权数据
201210157196.6 2012.05.18 CN

(62)分案原申请数据
201380018643.2 2013.05.17

(71)申请人 爱德迪安(北京)生物技术有限公司
地址 100081 北京市海淀区皂君东里38楼

(72)发明人 秦树林

(74)专利代理机构 北京信诺创成知识产权代理有限公司 11728
代理人 尹吉伟 陈悦军

(51)Int.Cl.
C07K 19/00(2006.01)
A61K 38/22(2006.01)
A61K 38/28(2006.01)
A61P 3/10(2006.01)
A61K 38/20(2006.01)

权利要求书21页 说明书117页
序列表182页 附图7页

(54)发明名称

用于糖尿病治疗的蛋白、蛋白缀合物及其应用

(57)摘要

本发明属于生物制药领域,涉及一种用于糖尿病治疗的蛋白、蛋白缀合物、药物组合物及其应用。本发明的融合蛋白由两种多肽通过连接而构成,其中一种多肽是白介素-1受体拮抗蛋白或其类似物,另一种多肽是GLP-1受体结合多肽或其类似物、或胰岛素受体结合多肽或其类似物、或GIP受体结合多肽或其类似物。本发明的融合蛋白及其缀合物具有明显的治疗糖尿病的功效,且用量少,对使用者的副作用明显降低。

CN 112142855 A

1.一种融合蛋白，所述融合蛋白由白介素-1受体拮抗蛋白或其类似物与另一种多肽连接而成，另一种多肽是胰岛素受体结合多肽或其类似物、或者GIP受体结合多肽或其类似物；

所述融合蛋白的结构为：白介素-1受体拮抗蛋白或其类似物-L_j-另一种多肽，或者另一种多肽-Lj-白介素-1受体拮抗蛋白或其类似物；

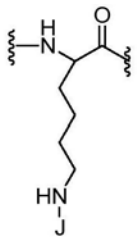
所述白介素-1受体拮抗蛋白或其类似物的序列是：

X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE，其中，

X_{IL0}是甲硫氨酸、半胱氨酸、通式1、通式2或缺失；

X_{IL66}、X_{IL69}、X_{IL116}、X_{IL122}是半胱氨酸或丝氨酸；X_{IL84}是半胱氨酸或天冬酰胺；

其中通式1的结构是：



其中，J是L_n-M_L结构、-W-X-Y-Z结构或氢原子；

M_L是修饰基团，包括但不局限于-W-X-Y-Z、脂肪酸、聚乙二醇、白蛋白、IgG Fc、糖基团；

L_n是可选的连接基、共价键或不存在；可选的连接基包括但不局限于：聚乙二醇、长链脂肪酸、多肽、天然或非天然氨基酸、或由一个或多个聚乙二醇分子、脂肪酸、多肽、氨基酸分子通过共价键连接形成的长链；

-W-X-Y-Z结构是：

W是侧链具有羧基的α-氨基酸残基，该残基以其羧基基团之一与多肽/蛋白N-末端氨基酸残基的α-氨基或与多肽/蛋白中的赖氨酸残基的ε-氨基或L_n末端的氨基一起形成酰胺基；

或者W是由2、3或4个α-氨基酸通过酰胺键连接起来的链，所述通过酰胺键连接的链连接至多肽/蛋白N-末端氨基酸残基的α-氨基或多肽/蛋白中赖氨酸残基的ε-氨基或L_n末端的氨基；W的氨基酸残基选自具有中性侧链的氨基酸残基和/或侧链具有羧基的氨基酸残基，使得W含有至少一个在侧链具有羧基的氨基酸残基；

或者W是从X到多肽/蛋白N-末端氨基酸的α-氨基或多肽/蛋白中的赖氨酸残基的ε-氨基或L_n末端的氨基的共价键；

X是-$\underline{C}$O-、-CH(COOH)$\underline{C}$O-、-N(CH_2COOH)$CH_2\underline{C}$O-、-N(CH_2COOH)CH_2CON(CH_2COOH)$CH_2\underline{C}$O-、-N(CH_2CH_2COOH)$CH_2CH_2\underline{C}$O-、-NHCH(COOH)$(CH_2)_4$NH$\underline{C}$O-、-N(CH_2CH_2COOH)CH_2CH_2CON(CH_2CH_2COOH)$CH_2CH_2\underline{C}$O-、-N(CH_2CH_2COOH)$CH_2\underline{C}$O-或者-N(CH_2COOH)$CH_2CH_2\underline{C}$O-，其中，

a)当W是氨基酸残基或氨基酸残基链时，上述X通过由加下划线的羰基碳的键与W中的氨基形成酰胺键；或者

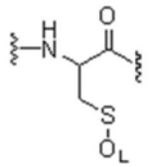
b)当W是共价键时，上述X通过来自加下划线的羰基碳的键与多肽/蛋白的N-末端氨基

酸残基的α-氨基或多肽/蛋白中的赖氨酸残基的ε-氨基或L_n末端的氨基形成酰胺键；

Y是-$(CH_2)_m$，其中m是6-32的整数；或包含1、2或3个-CH＝CH-基团和多个-CH_2-基团的二价烃链，所述多个-CH_2-基团的个数满足烃链中的碳原子总数范围是10-32；或通式-$(CH_2)_vC_6H_4(CH_2)_w$-的二价烃链，其中v和w是整数，或者它们之一是零，使得v和w总和的范围是6-30；且

Z是-COOH、-CO-Asp、-CO-Glu、-CO-Gly、-CO-Sar、-$CH(COOH)_2$、-$N(CH_2COOH)_2$、-SO_3H、-PO_3H或不存在；条件是当W是共价键且X是-CO-时，Z不是-COOH；

通式2的结构是：



其中，

O_L的基本结构是M_r-L_r-NH-J、M_r-L_r-Z_1、M_r-L_r-M_r或M_r-L_r-M_L或氢原子；

J和M_L如上文中所定义；

M_r是能够与巯基反应形成共价键的功能团；L_r是可选的连接基、共价键或不存在，包括但不局限于：聚乙二醇、长链脂肪酸、或由一个或多个聚乙二醇分子和长链脂肪酸分子通过共价键连接形成的长链化合物；

M_r-L_r-M_r中L_r两端的M_r可以相同，也可以不同；M_r-L_r-M_r通过一端的M_r与IL-1ra反应后形成共价键连接；

Z_1是-COOH、-CO-Asp、-CO-Glu、-CO-Gly、-CO-Sar、-$CH(COOH)_2$、-$N(CH_2COOH)_2$、-SO_3H、-PO_3H或不存在；m、n、p分别是1-25的整数；

L_j是连接基或间隔基，包括长链脂肪酸、聚乙二醇、氨基酸、短肽、蛋白，或一个或多个可选的长链脂肪酸、聚乙二醇、氨基酸、短肽等通过共价键连接而成的长链，或任何将两个蛋白/多肽通过共价键连接的结构，或缺失；优选地，所述连接基或间隔基含有一个或一个以上的赖氨酸或半胱氨酸，其侧链的氨基或巯基可用于与修饰基团反应；优选地，所述短肽的通式是$(GlyGlyGlyGlySer)_n$，n是0、1、2、3、4、5或6；

优选地，所述白介素-1受体拮抗蛋白或其类似物的序列是：

U_L-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE；或者，

U_L-CRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE；

U_L-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDEC；

CRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFY

FQEDE；

CRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；

CRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVCITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；

RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVCITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；

RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVCITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；

RPSGRCSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；

RPSGRCSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；

RPSGRKSCKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；

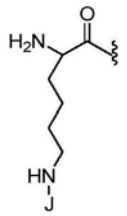
RPSGRKSCKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；

RPSGRKSSCMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；

RPSGRKSSCMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；或者，

RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGCMVTKFYFQEDE；

其中，U_L是-W-X-Y-Z结构、脂肪酸、聚乙二醇、白蛋白、IgG Fc、糖基团、氢原子或N^{α}-(N^{α}-(HOOC$(CH_2)_n$CO)-γ-Glu)-、N^{α}-(N^{α}-$(CH_3(CH_2)_n$CO)-γ-Glu)-，其中n是整数8-20，N^{α}表示氨基酸或氨基酸残基的α-氨基，或为通式5：



其中-W-X-Y-Z和J分别如上述所定义。

2.根据权利要求1所述的融合蛋白，所述另一种多肽是胰岛素受体结合多肽或其类似物，所述另一种多肽的序列是：

X_{IN107}HLC[1]GSX_{IN108}LVEALYLVC[2]GEX_{IN109}GF$X_{IN110}X_{IN111}X_{IN112}X_{IN113}X_{IN114}X_{IN115}$-$C_L$-GIVEQC[3]C[4]$X_{IN127}$SIC[5]SLYQLENYC[6]$X_{IN128}X_{IN129}$，其中，

X_{IN107}是苯丙氨酸-缬氨酸-天冬酰胺-谷氨酰胺四肽、缬氨酸-天冬酰胺-谷氨酰胺三肽、天冬酰胺-谷氨酰胺二肽、或谷氨酰胺，或是以赖氨酸或精氨酸取代二、三、四肽序列中任何一个氨基酸残基后的序列，或缺失；X_{IN108}是组氨酸、苯丙氨酸、精氨酸或谷氨酰胺；X_{IN109}是精氨酸、丙氨酸、谷氨酸或天冬氨酸；X_{IN110}是苯丙氨酸、酪氨酸或组氨酸；X_{IN111}是酪氨酸、苯丙氨酸或缺失；X_{IN112}是苏氨酸、天冬酰胺或缺失；X_{IN113}是脯氨酸、赖氨酸、谷氨酸、天冬氨酸或缺失；X_{IN114}是赖氨酸、脯氨酸、精氨酸、谷氨酸、天冬氨酸或缺失；X_{IN115}是苏氨酸或缺失；X_{IN127}是苏氨酸、组氨酸或精氨酸；X_{IN128}是丙氨酸、甘氨酸或天冬酰胺；X_{IN129}是赖氨酸、精氨酸-赖氨酸二肽或缺失；

C_L是6-60个氨基酸的肽序列，其中氨基酸主要选自由甘氨酸、丙氨酸、丝氨酸、苏氨酸、脯氨酸组成的组；

优选地，C_L是：G$X_{IN116}X_{IN117}X_{IN118}X_{IN119}X_{IN120}X_{IN121}X_{IN122}X_{IN123}X_{IN124}X_{IN125}$ X_{IN126}，其中，

X_{IN116}是赖氨酸、半胱氨酸、丝氨酸或丙氨酸；X_{IN117}是甘氨酸、赖氨酸或丝氨酸；X_{IN118}是赖氨酸或丝氨酸；X_{IN119}是赖氨酸或丝氨酸；X_{IN120}是赖氨酸、丝氨酸或丙氨酸；X_{IN121}是甘氨酸、赖氨酸、精氨酸、丙氨酸或脯氨酸或缺失；X_{IN122}是甘氨酸、丙氨酸、精氨酸、赖氨酸、谷氨酰胺或脯氨酸或缺失；X_{IN123}是精氨酸、赖氨酸、甘氨酸、丙氨酸、脯氨酸、苏氨酸或谷氨酰胺或缺失；X_{IN124}是脯氨酸、谷氨酰胺、赖氨酸、甘氨酸、精氨酸或缺失；X_{IN125}是谷氨酰胺、苏氨酸、赖氨酸、甘氨酸、精氨酸或缺失；X_{IN126}是苏氨酸、精氨酸、赖氨酸或缺失；

进一步优选地，C_L是GAGSSSAAAPQT、GSGSSSAAAPQT、GSGSSSAAPQT、GSGSSSAPQT或GSGSSAPQT；

或者胰岛素受体结合多肽包括A链和B链，其中，

A链的氨基酸序列为：GIVEQC[3]C[4]X_{IN8}SIC[5]SLYQLENYC[6]$X_{IN21}X_{IN22}$或

GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N；

B链氨基酸序列为：

$X_{IN23-26}$HLC[1]GSHLVEALYLVC[2]GERGF$X_{IN47}X_{IN48}X_{IN49}X_{IN50}X_{IN51}X_{IN52}$，其中，

X_{IN8}是苏氨酸、组氨酸或精氨酸；X_{IN21}是丙氨酸、甘氨酸或天冬酰胺；X_{IN22}是赖氨酸、精氨酸-赖氨酸二肽或缺失；$X_{IN23-26}$是苯丙氨酸-缬氨酸-天冬酰胺-谷氨酰胺四肽、缬氨酸-天冬酰胺-谷氨酰胺三肽、天冬酰胺-谷氨酰胺二肽、谷氨酰胺或缺失；X_{IN47}是酪氨酸或苯丙氨酸；X_{IN48}是-NH_2、dA-NH_2、酪氨酸或苯丙氨酸；X_{IN49}是苏氨酸、天冬酰胺或缺失；X_{IN50}是赖氨酸、脯氨酸、谷氨酸、天冬氨酸或缺失；X_{IN51}是脯氨酸、精氨酸、赖氨酸、谷氨酸、天冬氨酸或缺

失;X_{IN52}是苏氨酸、苏氨酸-精氨酸-精氨酸或缺失;

所述化合物中,[1]-[6]表示半胱氨酸的编号;所述化合物中通过6个半胱氨酸形成3对二硫键,其中A链和B链通过两对链间二硫键连接,A链内存在一对链内二硫键,三对二硫键的具体位置是:$C_{[1]}$和$C_{[4]}$形成二硫键,$C_{[2]}$和$C_{[6]}$形成二硫键,$C_{[3]}$和$C_{[5]}$形成二硫键;

或者胰岛素受体结合多肽包括A链和B链,其中,

A链的氨基酸序列为:

$GIVEQC_{[3]}C_{[4]}TSIC_{[5]}X_{IN412}LX_{IN414}X_{IN415}LX_{IN417}X_{IN418}YC_{[6]}X_{IN421}X_{IN422}$,

B链的氨基酸序列为:

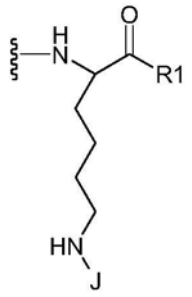
$X_{IN423-426}HLC_{[1]}GSHLVEALYLVC_{[2]}GERGFX_{IN447}X_{IN448}X_{IN449}X_{IN450}X_{IN451}X_{IN452}X_{IN453}$,

所述化合物中,[1]-[6]表示半胱氨酸的编号;所述化合物通过6个半胱氨酸形成3对二硫键,其中A链和B链通过两对链间二硫键连接,A链内存在一对链内二硫键,三对二硫键的具体位置是:$C_{[1]}$和$C_{[4]}$形成二硫键,$C_{[2]}$和$C_{[6]}$形成二硫键,$C_{[3]}$和$C_{[5]}$形成二硫键;

其中X_{IN412}为丝氨酸或通式1结构:X_{IN414}为酪氨酸或通式1结构;X_{IN415}是谷氨酰胺或通式1结构;X_{IN417}为谷氨酸或通式1结构;X_{IN418}为天冬酰胺或通式1结构;X_{IN421}为是天冬酰胺、丙氨酸或甘氨酸;X_{IN422}为赖氨酸、通式3、精氨酸-通式3或缺失;$X_{IN423-426}$是甘氨酸-脯氨酸-谷氨酸三肽、U_L-甘氨酸-脯氨酸-谷氨酸、苯丙氨酸-缬氨酸-天冬酰胺-谷氨酰胺四肽或U_L-苯丙氨酸-缬氨酸-天冬酰胺-谷氨酰胺;X_{IN447}是酪氨酸或苯丙氨酸;X_{IN448}是-NH_2、苯丙氨酸、酪氨酸或缺失;X_{IN449}是苏氨酸、天冬酰胺或缺失;X_{IN450}是赖氨酸、精氨酸、谷氨酸、天冬氨酸、脯氨酸或缺失;X_{IN451}是脯氨酸、赖氨酸、精氨酸、谷氨酸、天冬氨酸或缺失,或为通式1或通式3结构;X_{IN452}是苏氨酸、赖氨酸或缺失,或为通式1或通式3结构;X_{IN453}赖氨酸或缺失,或为通式3结构;

通式1、U_L如权利要求1所定义;

通式3的结构是:



,

J如权利要求1所定义;R_1是-OH或-NH_2。

3.根据权利要求2所述的融合蛋白,其特征在于,所述另一种多肽的序列是:

U_L-$X_{IN300}HLC_{[1]}GSHLVEALYLVC_{[2]}GERGFX_{IN301}X_{IN302}X_{IN303}X_{IN304}X_{IN305}X_{IN306}GX_{IN307}X_{IN308}X_{IN309}X_{IN310}X_{IN311}X_{IN312}X_{IN313}X_{IN314}X_{IN315}X_{IN316}X_{IN317}GIVEQC_{[3]}C_{[4]}X_{IN318}SIC_{[5]}X_{IN319}LX_{IN320}X_{IN321}LX_{IN322}X_{IN323}YC_{[6]}X_{IN324}X_{IN325}$,

U_L-$FVNQHLCGSHLVEALYLVCGERGFFX_{IN302}X_{IN303}X_{IN304}X_{IN305}X_{IN306}GX_{IN307}X_{IN308}X_{IN309}X_{IN310}X_{IN311}X_{IN312}X_{IN313}X_{IN314}X_{IN315}X_{IN316}X_{IN317}GIVEQCCTSICSLYQLENYCNX_{IN325}$,

U_L-$X_{IN107}HLC_{[1]}GSX_{IN108}LVEALYLVC_{[2]}GEX_{IN109}GFX_{IN110}X_{IN111}X_{IN112}X_{IN113}X_{IN114}X_{IN115}$-$C_L$-$GIVEQC_{[3]}C_{[4]}X_{IN127}SICSLYQLENYC_{[6]}X_{IN128}X_{IN129}$;或者,

U_L-X_{IN107}HLC[1]GSHLVEALYLVC[2]GERGFX$_{IN110}$X$_{IN111}$X$_{IN112}$X$_{IN113}$X$_{IN114}$X$_{IN115}$-C_L-GIVEQC[3]C[4]TSICSLYQLENYC[6]X$_{IN128}$X$_{IN129}$;或者，

U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$T-C_L-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;或者，

U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$TGKGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;或者，

U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$TGSGKSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;或者，

U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$TGSGSKSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;或者

U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$TGSGSSKAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;或者，

U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$TGSGSSSKAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;或者，

U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$TGSGSSSAKAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;或者，

U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$TGSGSSSAAKPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;或者，

U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$TGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NK;或者，

FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$TGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;或者，

U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAKPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;或者，

U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAKAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;或者，

U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSKAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;或者，

U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NK;或者，

FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;或者

FVNQHLC[1]GSHLVEALYLVC[2]GERGFFX$_{IN111}$X$_{IN112}$X$_{IN113}$X$_{IN114}$X$_{IN115}$-C_L-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N，其中，各变量如权利要求2所定义；

其中，

X$_{IN300}$是苯丙氨酸-缬氨酸-天冬酰胺-谷氨酰胺四肽、缬氨酸-天冬酰胺-谷氨酰胺三肽、天冬酰胺-谷氨酰胺二肽、谷氨酰胺、或是以赖氨酸或精氨酸取代二、三、四肽序列中任何一个氨基酸残基后的序列或缺失；X$_{IN301}$是苯丙氨酸、组氨酸或酪氨酸；X$_{IN302}$是-NH_2、酪氨酸、苯丙氨酸或缺失；X$_{IN303}$是苏氨酸、天冬酰胺或缺失；X$_{IN304}$是脯氨酸、赖氨酸、谷氨酸、天冬氨酸

或缺失;X_{IN305}是天冬氨酸、谷氨酸、脯氨酸、精氨酸、赖氨酸、缺失或通式1结构;X_{IN306}是苏氨酸、通式1结构或缺失;X_{IN307}是丝氨酸、丙氨酸、甘氨酸、赖氨酸、通式1结构或缺失;X_{IN308}是甘氨酸、通式1结构或缺失;X_{IN309}是赖氨酸、甘氨酸、丝氨酸、通式1结构或缺失;X_{IN310}是赖氨酸、甘氨酸、丝氨酸、通式1结构或缺失;X_{IN311}是赖氨酸、甘氨酸、丝氨酸、丙氨酸、通式1结构或缺失;X_{IN312}是赖氨酸、精氨酸、丙氨酸、脯氨酸、甘氨酸、通式1结构或缺失;X_{IN313}是甘氨酸、丙氨酸、精氨酸、赖氨酸、谷氨酰胺、脯氨酸、通式1结构或缺失;X_{IN314}是精氨酸、丙氨酸、脯氨酸、苏氨酸、谷氨酰胺、甘氨酸、通式1结构或缺失;X_{IN315}是脯氨酸、谷氨酰胺、精氨酸、甘氨酸、缺失或通式I结构;X_{IN316}是谷氨酰胺、苏氨酸、精氨酸、甘氨酸、缺失或通式1结构;X_{IN317}是苏氨酸、精氨酸、赖氨酸或缺失;X_{IN318}是苏氨酸、组氨酸、精氨酸或通式1结构;X_{IN319}是丝氨酸或通式1结构;X_{IN320}是酪氨酸或通式1结构;X_{IN321}是谷氨酰胺或通式1结构;X_{IN322}是谷氨酸或通式1结构;X_{IN323}是天冬酰胺或通式1结构;X_{IN324}是天冬氨酸、甘氨酸、丙氨酸或通式1结构;X_{IN325}是赖氨酸、通式3、精氨酸-通式3或缺失;

通式1、U_L如权利要求1所定义;通式3如权利要求2所定义。

4.根据权利要求2所述的融合蛋白,其特征在于,所述融合蛋白的序列是:

U_L-X_{IN107}HLC[1]GSX_{IN108}LVEALYLVC[2]GEX_{IN109}GF$X_{IN110}X_{IN111}X_{IN112}X_{IN113}X_{IN114}X_{IN115}$-$C_L$-GIVEQC[3]C[4]$X_{IN127}$SIC[5]SLYQLENYC[6]$X_{IN128}X_{IN129}$-$L_j$-$X_{IL0}$RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE,或者,

U_L-X_{IN107}HLC[1]GSHLVEALYLVC[2]GERGFX$_{IN110}X_{IN111}X_{IN112}X_{IN113}X_{IN114}X_{IN115}$-$C_L$-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N-(GGGGS)$_m$-X_L-(GGGGS)$_n$-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE,或者,

U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKT-C_L-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N-(GGGGS)$_m$-X_L-(GGGGS)$_n$-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE,或者,

U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKT-C_L-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N-(GGGGS)$_n$-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者,

U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE-L_j-X_{IN107}HLC[1]GSX_{IN108}LVEALYLVC[2]GEX_{IN109}GF$X_{IN110}X_{IN111}X_{IN112}X_{IN113}X_{IN114}X_{IN115}$-$C_L$-GIVEQC[3]C[4]$X_{IN127}$SIC[5]SLYQLENYC[6]$X_{IN128}X_{IN129}$;或者,

U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_m$-X_L-(GGGGS)$_n$-X_{IN107}HLC[1]GSHLVEALYLVC[2]GERGFX$_{IN110}X_{IN111}X_{IN112}X_{IN113}X_{IN114}X_{IN115}$-$C_L$-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]$X_{IN128}X_{IN129}$;或者,

U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGK

$MX_{IL66}LSX_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX_{IL116}PGWFLX_{IL122}TAMEAD QPVSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_m$-X_L-(GGGGS)$_n$-FVNQHLC[1]GSHLVEALYLVC[2] GERGFFYTPKT-C_L-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;或者，

U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGK $MX_{IL66}LSX_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX_{IL116}PGWFLX_{IL122}TAMEAD QPVSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_n$-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKT-C_L-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;或者，

U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGK $MX_{IL66}LSX_{IL69}$VKSGDETRLQLEAVX_{IL84}ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX_{IL116}PGWFLX_{IL122}TAM EADQPVSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_m$-X_L-(GGGGS)$_n$-FVNQHLCGSHLVEALYLVCGERGFFYTP KTGSGSSSAAAPQTGIVEQCCTSICSLYQLENYCN;或者，

U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGK $MX_{IL66}LSX_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(连接基-胰岛素受体结合多肽)PGWFLX_{IL122}TAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者，

U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGK $MX_{IL66}LSX_{IL69}$VKSGDETRLQLEAVC(连接基-胰岛素受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPT TSFESAASPGWFLX_{IL122}TAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者，

(胰岛素受体结合多肽-连接基)-C_{IL0}-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQG PNVNLEEKIDVVPIEPHALFLGIHGGK$MX_{IL66}LSX_{IL69}$VKSGDETRLQLEAVX_{IL84}ITDLSENRKQDKRFAFIRSDS GPTTSFESAAX_{IL116}PGWFLX_{IL122}TAMEADQPVSLTNMPDEGVMVTKFYFQEDE，

U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGK $MX_{IL66}LSX_{IL69}$VKSGDETRLQLEAVX_{IL84}ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX_{IL116}PGWFLX_{IL122}TAM EADQPVSLTNMPDEGVMVTKFYFQEDEC$_{IL153}$(连接基-胰岛素受体结合多肽)，

(胰岛素受体结合多肽-连接基)RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEK IDVVPIEPHALFLGIHGGK$MX_{IL66}LSX_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESA AX_{IL116}PGWFLX_{IL122}TAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者，

(胰岛素受体结合多肽-连接基)CRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEE KIDVVPIEPHALFLGIHGGK$MX_{IL66}LSX_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAA SPGWFLX_{IL122}TAMEADQPVSLTNMPDEGVMVTKFYFQEDE；

其中，m、n是0、1、2、3、4、5或6；X_L是半胱氨酸、赖氨酸、缺失、通式1或通式2；C_{IL0}、C_{IL153}是半胱氨酸或缺失；[1]-[6]表示半胱氨酸的编号；所述化合物中通过6个半胱氨酸形成3对二硫键，三对二硫键的具体位置是：C[1]和C[4]形成二硫键，C[2]和C[6]形成二硫键，C[3]和C[5]形成二硫键；

通式1、通式2和U_L如权利要求1所定义。

5.根据权利要求2所述的融合蛋白，其特征在于，胰岛素受体结合多肽与白介素-1受体拮抗蛋白与生物大分子形成单链化合物，所述融合蛋白的结构为(从左到右对应氨基酸序列从N末端到C末端)：

胰岛素受体结合多肽-连接基(或间隔基)-生物大分子-连接基(或间隔基)-白介素-1受体拮抗蛋白；

胰岛素受体结合多肽-连接基(或间隔基)-白介素-1受体拮抗蛋白-连接基(或间隔基)-生物大分子;

生物大分子-连接基(或间隔基)-胰岛素受体结合多肽-连接基(或间隔基)-白介素-1受体拮抗蛋白;

生物大分子-连接基(或间隔基)白介素-1受体拮抗蛋白-连接基(或间隔基)-胰岛素受体结合多肽;

白介素-1受体拮抗蛋白-连接基(或间隔基)-生物大分子-连接基(或间隔基)-胰岛素受体结合多肽;或者

白介素-1受体拮抗蛋白-连接基(或间隔基)-胰岛素受体结合多肽-连接基(或间隔基)-生物大分子;

其中生物大分子是白蛋白或IgG Fc。

6.根据权利要求5所述的融合蛋白,其特征在于,包含人白蛋白的融合蛋白序列为:

DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGD
KLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPY
FYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFP
KAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPA
DLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDE
FKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDY
LSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTA
LVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL-(GGGGS)$_m$-FVNQHLC[1]
GSHLVEALYLVC[2]GERGFFYTPKT-C_L-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N-(GGGGS)$_n$-RPSGRKSSK
MQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQL
EAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQ
EDE;或

DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGD
KLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPY
FYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFP
KAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPA
DLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDE
FKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDY
LSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTA
LVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL-(GGGGS)$_m$-RPSGRKSSK
MQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQL
EAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQ
EDE-(GGGGS)$_n$-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKT-C_L-GIVEQC[3]C[4]TSIC[5]
SLYQLENYC[6]N;或者,

FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKT-C_L-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N-
(GGGGS)$_m$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLH
TLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIA

RRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARL
SQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVEN
DEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYA
KVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMP
CAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQI
KKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL-(GGGGS)$_n$-RPSG
RKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDE
TRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVT
KFYFQEDE;或者，

FVNQHLC$_{[1]}$GSHLVEALYLVC$_{[2]}$GERGFFYTPKT-C$_L$-GIVEQC$_{[3]}$C$_{[4]}$TSIC$_{[5]}$SLYQLENYC$_{[6]}$N-
(GGGGS)$_m$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL6}$
$_6$LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVS
LTNMPDEGVMVTKFYFQEDE-(GGGGS)$_n$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEV
TEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDV
MCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRL
KCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSK
LKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLA
KTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEV
SRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEF
NAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAA
SQAALGL;或者，

FVNQHLC$_{[1]}$GSHLVEALYLVC$_{[2]}$GERGFFYTPKTGSGSSSAAAPQTGIVEQC$_{[3]}$C$_{[4]}$TSIC$_{[5]}$
SLYQLENYC$_{[6]}$NGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPH
ALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWF
LX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDEGGGGSGGGGSDAHKSEVAHRFKDLGEENFKALVLIAFAQYL
QQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKD
DNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLD
ELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRAD
LAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYA
RRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRY
TKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPC
FSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADD
KETCFAEEGKKLVAASQAALGL;或者，

X$_{IL0}$RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$L
SX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLT
NMPDEGVMVTKFYFQEDE-(GGGGS)$_m$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTE
FAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMC
TAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKC
ASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLK

ECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKT
YETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSR
NLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNA
ETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQ
AALGL-(GGGGS)$_n$-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKT-C_L-GIVEQC[3]C[4]TSIC[5]
SLYQLENYC[6]N;或者，

X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$L
SX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLT
NMPDEGVMVTKFYFQEDE-(GGGGS)$_m$-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKT-C_L-GIVEQC[3]C[4]
TSIC[5]SLYQLENYC[6]N-(GGGGS)$_n$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTE
FAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMC
TAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKC
ASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLK
ECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKT
YETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSR
NLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNA
ETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQ
AALGL;

其中，上述各融合蛋白中，m、n是0、1、2、3、4、5或6，其它各变量如权利要求1所定义。

7.根据权利要求2所述的融合蛋白，其特征在于，其为白介素-1受体拮抗蛋白-连接基或间隔基-胰岛素受体结合多肽二聚蛋白/交联蛋白，其中用于形成二聚蛋白/交联蛋白的白介素-1受体拮抗蛋白是：

U_L-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$L
SX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPV
SLTNMPDEGVMVTKFYFQEDE;或者，

U_L-CRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$
LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLX$_{IL122}$TAMEADQPVSLTNM
PDEGVMVTKFYFQEDE;或者，

U_L-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$L
SX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLX$_{IL122}$TAMEADQPVSLTNMP
DEGVMVTKFYFQEDEC;

各蛋白中的各变量以及U_L如权利要求1中所定义。

8.根据权利要求2～7任意一项所述的融合蛋白，其特征在于，所述融合蛋白选自化合物IN-1～IN70。

9.根据权利要求1所述的融合蛋白，其特征在于，所述另一种多肽是GIP受体结合多肽或其类似物，所述另一种多肽的序列是：

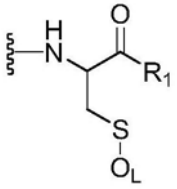
(X$_{GI1}$X$_{GI2}$X$_{GI3}$GT)$_{t0}$X$_{GI6}$X$_{GI7}$SDX$_{GI10}$SX$_{GI12}$X$_{GI13}$X$_{GI14}$DX$_{GI16}$X$_{GI17}$X$_{GI18}$QX$_{GI20}$X$_{GI21}$FX$_{GI23}$X$_{GI24}$WLX$_{GI27}$X$_{GI28}$X$_{GI29}$X$_{GI30}$X$_{GI31}$X$_{GI32}$X$_{GI33}$X$_{GI34}$X$_{GI35}$X$_{GI36}$X$_{GI37}$X$_{GI38}$X$_{GI39}$X$_{GI40}$X$_{GI41}$X$_{GI42}$X$_{GI43}$，其中，

X$_{GI1}$是酪氨酸、N-乙酰基酪氨酸、焦谷氨酰-酪氨酸、葡萄糖醇-酪氨酸、D-组氨酸、α，α-2

甲基咪唑乙酸(DMIA)、N-甲基组氨酸、α-甲基组氨酸、咪唑乙酸、脱氨组氨酸、羟基组氨酸、乙酰组氨酸、高组氨酸、N-棕榈酸-酪氨酸、N-Fmoc-酪氨酸或缺失;X_{GI2}是丙氨酸、D-丙氨酸、D-丝氨酸、丝氨酸、缬氨酸、甘氨酸、N-甲基丝氨酸、N-甲基丙氨酸、2-甲基丙氨酸或缺失;X_{GI3}是谷氨酸、羟基脯氨酸、脯氨酸或缺失;X_{GI6}是苯丙氨酸或缺失;X_{GI7}是异亮氨酸或苏氨酸;X_{GI10}是酪氨酸、色氨酸、苯丙氨酸、缬氨酸、赖氨酸、鸟氨酸、谷氨酸、亮氨酸、通式1或通式2;X_{GI12}是异亮氨酸、丝氨酸、赖氨酸、精氨酸、通式1或通式2;X_{GI13}是丙氨酸、谷氨酰胺或酪氨酸;X_{GI14}是甲硫氨酸或亮氨酸;X_{GI16}是赖氨酸、精氨酸、丝氨酸、谷氨酸、谷氨酰胺、高谷氨酸、高半胱氨酸、苏氨酸、甘氨酸、2-甲基丙氨酸、通式1或通式2;X_{GI17}是异亮氨酸、谷氨酰胺、谷氨酸、精氨酸、通式1或通式2;X_{GI18}是组氨酸、丙氨酸、精氨酸、丝氨酸、苏氨酸或甘氨酸;X_{GI20}是谷氨酰胺、赖氨酸、丙氨酸、丝氨酸、苏氨酸、瓜氨酸、精氨酸、鸟氨酸、2-甲基丙氨酸、其它α,α-双取代氨基酸、通式1或通式2;X_{GI21}是天冬氨酸、谷氨酸、高谷氨酸、高半胱氨酸、亮氨酸、通式1或通式2;X_{GI23}是缬氨酸或异亮氨酸;X_{GI24}是谷氨酰胺、谷氨酸、天冬酰胺、丙氨酸、丝氨酸、苏氨酸、2-甲基丙氨酸、通式1或通式2;X_{GI27}是亮氨酸、异亮氨酸、正亮氨酸、赖氨酸、缬氨酸、甲硫氨酸、通式1或通式2;X_{GI28}是甘氨酸、丙氨酸、赖氨酸、天冬酰胺、通式1或通式2;X_{GI29}是谷氨酰胺、甘氨酸、苏氨酸、丙氨酸、通式1或通式2;X_{GI30}是赖氨酸、精氨酸、甘氨酸、通式1或通式2;X_{GI31}是-NH_2、甘氨酸、脯氨酸或缺失;X_{GI32}是赖氨酸、精氨酸、丝氨酸、通式1、通式2或缺失;X_{GI33}是赖氨酸、精氨酸、丝氨酸、通式1、通式2或缺失;X_{GI34}是天冬酰胺、甘氨酸或缺失;X_{GI35}是天冬酰胺、丙氨酸或缺失;X_{GI36}是色氨酸、脯氨酸或缺失;X_{GI37}是赖氨酸、精氨酸、脯氨酸、通式1、通式2或缺失;X_{GI38}是组氨酸、脯氨酸或缺失;X_{GI39}是天冬酰胺、丝氨酸或缺失;X_{GI40}是异亮氨酸、-NH_2、通式1、通式2或缺失;X_{GI41}是苏氨酸或缺失;X_{GI42}是谷氨酰胺或缺失;X_{GI43}是赖氨酸、半胱氨酸、PSSGAPPPS、通式3、通式4或缺失;t0是0或1;

其中通式1和通式2如权利要求1所定义,通式3如权利要求2所定义,

通式4的结构是:



R_1是-OH或-NH_2,O_L如权利要求1所定义;

优选地,所述另一种多肽的序列是:

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQC;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWCHNITQ;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQKGKCNDWKHNITQ;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQKGCKNDWKHNITQ;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQCGKKNDWKHNITQ;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDCIHQQDFVNWLLAQKGKKNDWKHNITQ;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSCAMDKIHQQDFVNWLLAQKGKKNDWKHNITQ;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDCSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQ;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQKC;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDCIHQQDFVNWLLAQK-NH_2;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQKPSSGAPPPSC;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQKPSSGAPPPC-NH_2;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQCPSSGAPPPS-NH_2;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDCIHQQDFVNWLLAQKPSSGAPPPS-NH_2;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSCAMDKIHQQDFVNWLLAQKPSSGAPPPS-NH_2;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDCSIAMDKIHQQDFVNWLLAQKPSSGAPPPS-NH_2;

FISDYSIAMDKIHQQDFVNWLLAQKC;

FISDYSIAMDKIHQQDFVNWLLAQC-NH_2;

FISDYSIAMDCIHQQDFVNWLLAQK-NH_2;

ISDYSIAMDKIHQQDFVNWLLAQC-NH_2;

ISDYSIAMDCIHQQDFVNWLLAQK-NH_2;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDRIHQQDFVNWLLAQRGRRNDWRHNITQK;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDRIHQQDFVNWLLAQRGRRNDWKHNITQ;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDRIHQQDFVNWLLAQRGRKNDWRHNITQ;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDRIHQQDFVNWLLAQRGKRNDWRHNITQ;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDRIHQQDFVNWLLAQKGRRNDWRHNITQ;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQRGRRNDWRHNITQ;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSKAMDRIHQQDFVNWLLAQRGRRNDWRHNITQ;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDKSIAMDRIHQQDFVNWLLAQRGRRNDWRHNITQ;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDRIHQQDFVNWLLAQRPSSGAPPPSK;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDRIHQQDFVNWLLAQRPSSGAPPPK-NH_2;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDRIHQQDFVNWLLAQKPSSGAPPPS-NH_2;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQRPSSGAPPPS-NH_2;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDKSIAMDRIHQQDFVNWLLAQRPSSGAPPPS-NH_2;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDRIHQQDFVNWLLAQK-NH_2;

$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQR-NH_2;

FISDYSIAMDRIHQQDFVNWLLAQK-NH_2;

FISDYSIAMDKIHQQDFVNWLLAQR-NH_2;

ISDYSIAMDRIHQQDFVNWLLAQK-NH_2;或者,

ISDYSIAMDKIHQQDFVNWLLAQR-NH_2;

或者所述另一种多肽的序列是U_L-$(X_{GI1}X_{GI2}X_{GI3}GT)_{t0}X_{GI6}ISDX_{GI10}SX_{GI12}AMDX_{GI16}$IHQQDFVNWL$X_{GI27}X_{GI28}QX_{GI30}$$(GX_{GI32}X_{GI33}NDWX_{GI37}HNITQ)_{t1}$$(PSSGAPPPS)_{t2}$,各变量上述所定义,$U_L$如权利要求1所定义,t0、t1、t2分别是0或1。

10.根据权利要求9所述的融合蛋白,其特征在于,所述融合蛋白的序列是:

U_L-$(X_{GI1}X_{GI2}X_{GI3}GT)_{t0}X_{GI6}X_{GI7}SDX_{GI10}SX_{GI12}X_{GI13}X_{GI14}DX_{GI16}X_{GI17}X_{GI18}QX_{GI20}X_{GI21}FX_{GI23}X_{GI24}WLX_{GI27}X_{GI28}X_{GI29}X_{GI30}X_{GI31}X_{GI32}X_{GI33}X_{GI34}X_{GI35}X_{GI36}X_{GI37}X_{GI38}X_{GI39}X_{GI40}X_{GI41}X_{GI42}X_{GI43}$-$L_j$-$X_{IL0}$RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX_{IL66}LSX_{IL69}VKSGDETRLQLEAVX_{IL84}ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX_{IL116}PGWFLX_{IL122}TAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者,

U_L-($X_{GI1}X_{GI2}X_{GI3}$GT)$_{t0}$$X_{GI6}$ISDX$_{GI10}SX_{GI12}$AMDX$_{GI16}$IHQQDFVNWLX$_{GI27}X_{GI28}QX_{GI30}$($GX_{GI32}X_{GI33}$NDWX$_{GI37}$HNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$-(GGGGS)$_m$-$X_L$-(GGGGS)$_n$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者，

U_L-$X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$-(GGGGS)$_m$-X_L-(GGGGS)$_n$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者，

U_L-X_{GI6}ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$-(GGGGS)$_m$-X_L-(GGGGS)$_n$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者，

U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(连接基-GIP受体结合多肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者，

U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(连接基-GIP受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者，

(GIP-1受体结合多肽-连接基)-C_{IL0}-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者，

U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDEC$_{IL153}$(连接基-GIP受体结合多肽)；

其中，m、n分别是0、1、2、3、4、5或6；t0、t1、t2分别是0或1；C_{IL0}是半胱氨酸或缺失；C_{IL153}是半胱氨酸或缺失；U_L如权利要求1所定义。

11.根据权利要求9所述的融合蛋白，其特征在于，GIP受体结合多肽与白介素-1受体拮抗蛋白与生物大分子形成单链化合物，所述融合蛋白的结构为(从左到右对应氨基酸序列从N末端到C末端)：

GIP受体结合多肽-连接基(或间隔基)-生物大分子-连接基(或间隔基)-白介素-1受体拮抗蛋白；

GIP受体结合多肽-连接基(或间隔基)-白介素-1受体拮抗蛋白-连接基(或间隔基)-生物大分子；

其中生物大分子是白蛋白或IgG Fc。

12.根据权利要求11所述的融合蛋白，其特征在于，包含人白蛋白的融合蛋白的序列为：

($X_{GI1}X_{GI2}X_{GI3}$GT)$_{t0}$$X_{GI6}$ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$-(GGGGS)$_m$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIA

RRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARL
SQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVEN
DEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYA
KVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMP
CAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQI
KKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL-(GGGGS)$_n$-RPSG
RKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQL
EAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;

或者包含人白蛋白的融合蛋白的序列为：

($X_{GI1}X_{GI2}X_{GI3}$GT)$_{t0}X_{GI6}$ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$-(GGGGS)$_m$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCL
SCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMV
TKFYFQEDE-(GGGGS)$_n$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADE
SAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEET
FLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGER
AFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLE
KSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCC
AAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKC
CKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADI
CTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL;

或者包含人白蛋白的融合蛋白的序列为：

($X_{GI1}X_{GI2}X_{GI3}$GT)$_{t0}X_{GI6}$ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$($X_{GI1}X_{GI2}X_{GI3}$GT)$_{t0}X_{GI6}$ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$-(GGGGS)$_m$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCL
SCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMV
TKFYFQEDE-(GGGGS)$_n$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADE
SAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEET
FLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGER
AFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLE
KSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCC
AAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKC
CKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADI
CTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL;

或者包含人白蛋白的融合蛋白的序列为：

($X_{GI1}X_{GI2}X_{GI3}$GT)$_{t0}X_{GI6}$ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$($X_{GI1}X_{GI2}X_{GI3}$GT)$_{t0}X_{GI6}$ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$-(GGGGS)$_m$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLH
TLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIA
RRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARL

SQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVEN
DEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYA
KVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMP
CAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQI
KKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL-(GGGGS)$_n$-RPSG
RKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQL
EAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;

或者包含IgG1 Fc的融合蛋白的序列为：

($X_{GI1}X_{GI2}X_{GI3}$GT)$_{t0}X_{GI6}$ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$-
(GGGGS)$_m$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCL
SCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMV
TKFYFQEDE-(GGGGS)$_n$-AEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF
SCSVMHEALHNHYTQKSLSLSPGK;

或者包含IgG1 Fc的融合蛋白的序列为：

($X_{GI1}X_{GI2}X_{GI3}$GT)$_{t0}X_{GI6}$ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$-
(GGGGS)$_m$-AEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
NHYTQKSLSLSPGK-(GGGGS)$_n$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIE
PHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEAD
QPVSLTNMPDEGVMVTKFYFQEDE;

其中，m、n分别是0、1、2、3、4、5或6；t0、t1、t2分别是0或1；其它变量如权利要求9所定义；

或者包含IgG1 Fc的融合蛋白是二聚蛋白，通过两个单体蛋白Fc部分的半胱氨酸形成链间二硫键，所述二聚蛋白是由两个相同序列组成的同型二聚体，每个加下划线的半胱氨酸C与另外一个单体对应位置的半胱氨酸形成链间二硫键，每个单体的Ca之间形成链间二硫键，每个单体的Cb之间形成链间二硫键；

优选地，IgG4 Fc与白介素-1受体拮抗蛋白的融合蛋白的序列为：(XGI1XGI2XGI3GT)
t0XGI6ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)t1(PSSGAPPPS)$_{t2}$-(GGGGS)$_m$-RPSGRKSS
KMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVN
ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE-
(GGGGS)$_n$-AESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTC$_a$VVVDVSQEDPEVQFNWYVDGVEV
HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC$_a$KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
KNQVSLTC$_b$LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSC$_b$SVMHEALHN
HYTQKSLSLSLG。

13.根据权利要求9-12任一项所述的融合蛋白，其特征在于，所述融合蛋白选自化合物GI-1～GI-30。

14.一种融合蛋白,其中GLP-1受体结合多肽与白介素-1受体拮抗蛋白与生物大分子形成单链化合物,所述融合蛋白的结构为(从左到右对应氨基酸序列从N末端到C末端):

GLP-1受体结合多肽-连接基(或间隔基)-生物大分子-连接基(或间隔基)-白介素-1受体拮抗蛋白;

GLP-1受体结合多肽-连接基(或间隔基)-白介素-1受体拮抗蛋白-连接基(或间隔基)-生物大分子;其中生物大分子是白蛋白或IgG Fc;

优选地,包含人白蛋白融合蛋白的序列为:

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-(GGGGS)$_m$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL-(GGGGS)$_n$-X$_{IL0}$RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE,其中,m、n分别是0、1、2、3、4、5或6;其它变量如本文中所定义的;

或人白蛋白融合蛋白的序列为:

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-(GGGGS)$_m$-X$_{IL0}$RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_n$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL,其中,m、n分别是0、1、2、3、4、5或6;其它变量如本文中所定义的;

或人白蛋白融合蛋白的序列为:

HX$_{G2}$EGTFTSDVSSYLEX$_{G16}$QAAKEFIAWLVKGRG-(GGGGS)$_m$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALL

VRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNR RPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCK ADDKETCFAEEGKKLVAASQAALGL-(GGGGS)$_n$-X$_{IL0}$RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGP NVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESA ACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE,其中,m、n分别是0、1、2、3、4、5或6;其它变量如本文中所定义的;

或人白蛋白融合蛋白的序列为:

HX$_{G2}$EGTFTSDVSSYLEX$_{G16}$QAAKEFIAWLVKGRG-(GGGGS)$_m$-X$_{IL0}$RPSGRKSSKMQAFRIWDVNQKTFYL RNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFI RSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_n$-DAHKSEVAHRFKDLG EENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCC AKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTE CCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHT ECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNY AEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELF EQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSD RVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAV MDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL,其中,m、n分别是0、1、2、3、4、5或6;其它变量如本文所定义;

或人白蛋白融合蛋白的序列为:

HX$_{G2}$EGTFTSDVSSYLEX$_{G16}$QAAKEFIAWLVKGRHX$_{G2}$EGTFTSDVSSYLEX$_{G16}$QAAKEFIAWLVKGR-(GGGGS)$_m$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCL SCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMV TKFYFQEDE-(GGGGS)$_n$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADE SAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEET FLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGER AFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLE KSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCC AAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKC CKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADI CTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL,其中,m、n分别是0、1、2、3、4、5或6;其它变量如本文中所定义的;

或人白蛋白融合蛋白的序列为:

HX$_{G2}$EGTFTSDVSSYLEX$_{G16}$QAAKEFIAWLVKGRHX$_{G2}$EGTFTSDVSSYLEX$_{G16}$QAAKEFIAWLVKGR-(GGGGS)$_m$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLH TLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIA RRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARL SQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVEN DEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYA

KVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMP
CAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQI
KKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL-(GGGGS)$_n$-RPSG
RKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQL
EAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;其
中,m、n分别是0、1、2、3、4、5或6;其它变量如本文中所定义的;

或人白蛋白融合蛋白的序列为:

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGG(PSSGAPPPS)$_{t2}$HGEGTFTSDLSKQMEEEAVRLFIEWLKNGG
(PSSGAPPPS)$_{t2}$-(GGGGS)$_m$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPH
ALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQP
VSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_n$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVN
EVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEV
DVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQ
RLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSIS
SKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLR
LAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLV
EVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPK
EFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLV
AASQAALGL,其中,m、n分别是0、1、2、3、4、5或6;t2是0或1;其它变量如本文中所定义的;

或人白蛋白融合蛋白的序列为:

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGG(PSSGAPPPS)$_{t2}$HGEGTFTSDLSKQMEEEAVRLFIEWLKNGG
(PSSGAPPPS)$_{t2}$-(GGGGS)$_m$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCV
ADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDN
EETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKF
GERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKP
LLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLE
KCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVG
SKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFH
ADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL-
(GGGGS)$_n$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCL
SCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMV
TKFYFQEDE,其中,m、n分别是0、1、2、3、4、5或6;t2是0或1;

IgG1 Fc融合蛋白的序列为:

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-(GGGGS)$_m$-X$_{IL0}$RPSGRKSSKMQAFRIWDVNQK
TFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKR
FAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_n$-AEPKSCDKTHT
CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK,其中,

其中，m、n分别是0、1、2、3、4、5或6；X_{IL0}是甲硫氨酸、半胱氨酸、通式1、通式2或缺失；通式1、通式2如权利要求1所定义；

或IgG1 Fc融合蛋白的序列为：

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-$(GGGGS)_m$-AEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK-$(GGGGS)_n$-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE，其中，m、n分别是0、1、2、3、4、5或6；X_{IL0}是甲硫氨酸、半胱氨酸、通式1、通式2或缺失；通式1、通式2如权利要求1所定义；

或IgG1 Fc融合蛋白的序列为：

HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGRG-$(GGGGS)_m$-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE-$(GGGGS)_n$-AEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK，其中，m、n分别是0、1、2、3、4、5或6；其它变量分别如本文中所定义的；

或IgG1 Fc融合蛋白的序列为：

HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGRG-$(GGGGS)_m$-AEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK-$(GGGGS)_n$-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE，其中m、n分别是0、1、2、3、4、5或6；其它变量分别如本文中所定义的；

或者所述融合蛋白是由两个相同序列组成的同型二聚体，通过两个单体蛋白的Fc部分的半胱氨酸形成的链间二硫键，其中，IgG4 Fc与白介素-1受体拮抗蛋白的融合蛋白单体的序列为：

HX_{G2}EGTFTSDVSSYLEEQAAKEFIAWLVKGGG-$(GGGGS)_m$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE-$(GGGGS)_n$-AESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTC$_a$VVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC$_a$KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTC$_b$LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSC$_b$SVMHEALHNHYTQKSLSLSLG，其中m、n分别是0、1、2、3、4、5或6；其它变量如上文中所定义的；

或者是由两个相同上述序列组成的同型二聚体，每个加下划线的半胱氨酸C与另外一个单体对应位置的半胱氨酸形成链间二硫键；每个单体的C_a之间形成链间二硫键；每个单

体的C_b之间形成链间二硫键，其中，IgG4 Fc与白介素-1受体拮抗蛋白的融合蛋白单体的序列为：

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGG-$(PSSGAPPPS)_{t2}$-$(GGGGS)_m$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE-$(GGGGS)_n$-AESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTC$_a$VVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC$_a$KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTC$_b$LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSC$_b$SVMHEALHNHYTQKSLSLSLG，其中，m、n分别是0、1、2、3、4、5或6；其它变量如本文中所定义的。

15.一种蛋白缀合物，其特征在于，所述蛋白缀合物是在权利要求1～14任一项所述的融合蛋白基础上进行酰化、接枝等修饰而获得的化合物。

16.一种药物组合物，包括权利要求1～14任一项所述的融合蛋白，或权利要求15所述的蛋白缀合物，以及制药学可接受的载体或添加剂。

17.根据权利要求1～14任一项所述的融合蛋白、或根据权利要求15所述的蛋白缀合物在制备治疗糖尿病的药物中的应用。

用于糖尿病治疗的蛋白、蛋白缀合物及其应用

[0001] 本申请是申请号为201380018643.2、申请日为2013年5月17日、发明名称为“用于糖尿病治疗的蛋白、蛋白缀合物及其应用”的发明专利申请的分案申请。

技术领域

[0002] 本发明属于生物制药领域，涉及一种用于糖尿病治疗的蛋白、蛋白缀合物及其应用。

背景技术

[0003] 细胞因子是细胞内存在或分泌的有生物活性的大分子，大多为多肽类物质，如各种白介素、干扰素、集落刺激因子(CSF)、肿瘤坏死因子(TNF)。在正常机体内低表达或不表达，在异常状态(疾病、防御)时转录、翻译。细胞因子调节或修饰炎症或免疫反应中的细胞应答。它们通过与敏感细胞表面的特殊受体结合而激活生物应答。细胞因子往往在多种靶细胞上都有受体，因此反应多效性是细胞因子的普遍性质。同时，也可通过其它细胞因子或细胞因子受体产生第二介导。

[0004] 对于一个高活性的细胞因子，必须存在控制其释放和限制其活性的机制。细胞因子的生物合成和释放可以通过其它细胞因子或外源因素来严格调节。现已发现了两种控制其活性的机制：一是受体拮抗剂(I型抑制蛋白)，它的结构与细胞因子同源，能与受体分子结合而不激发信号的传导，通过与细胞因子竞争而产生抑制作用；二是可溶性受体分子(Ⅱ型抑制蛋白)，它同细胞受体竞争与细胞因子结合，从而产生抑制作用。大量实验证明这两种抑制反应有生理相关性。现在认为Ⅱ型抑制剂有着类似缓冲液的中和作用，从而限制细胞因子的全身作用。同时又允许细胞因子在局部达到高浓度，从而加强旁分泌样的作用。它们的重组表达形式具有药理活性。

[0005] 白细胞介素1(IL-1)参与多种生理过程。IL-1通过诱发中性蛋白酶和其它细胞因子(肿瘤坏死因子TNF)的分泌，刺激各种造血细胞和其它细胞的增生，调节促炎反应，介导炎症中的组织损伤，包括刺激滑膜细胞和软骨细胞增殖并产生PGE2、胶原酶、磷脂酶A等，引起关节炎症；促进骨髓释放中性粒细胞，诱导单核细胞和多核粒细胞趋化浸润到炎性部位，在局部释放溶酶体酶，引起嗜碱性粒细胞和肥大细胞脱颗粒，释放炎性介质等。IL-1可以直接损害胰岛中生产胰岛素的β细胞。与IL-1相关的疾病包括：类风湿性关节炎、糖尿病、系统性红斑狼疮、硬皮病等其他免疫性疾病。

[0006] IL-1包括两个相关因子：IL-1α和IL-1β。另外还有一种相关多肽为IL-1受体拮抗剂(IL-1Ra)。IL-1α、IL-1β均是通过与细胞表面的IL-1受体(IL-1R)结合，通过信号转导系统将信号传入细胞内发挥其生物活性。现已发现了两种类型的IL-1R：I型受体(IL-1RI)和Ⅱ型受体(IL-1RⅡ)。I型受体，又称T细胞受体，具有信号转导功能；Ⅱ型受体，又称B细胞受体，它可以和IL-1结合，但不转导信号。事实上，IL-1RⅡ承担了IL-1衰减子的作用，可称之为“诱捕”受体。当IL-1结合IL-1RI时，即形成一个复合物，然后该复合物即与IL-1R附属蛋白(LI-1R AcP)形成一种高亲和力的结合。可能是由于IL-1RI胞内部分与IL-1R-AcP结合形

成的异源二聚体激发了IL-1信号的转导。另外，IL-1R的胞外部分，又称为可溶性受体，即Ⅰ型可溶性受体(sIL-1RⅠ)和Ⅱ型可溶性受体(sIL-1RⅡ)，它们在机体的正常状态和疾病情况下均存在于循环体系中，可与IL-1α、IL-1β或IL-1Ra结合而成为一种天然的"缓冲剂"。

[0007] Arend等("Interleukin 1receptor antagonist:A new member of the interleukin 1family."J Clin Invest,1991,88(5):1445-1451)发现在细胞培养上清液和体液中有抑制IL-1活性的物质，将其命名为IL-1Ra。Eisenberg等("Interleukin 1receptor antagonist is a member of the interleukin 1gene family:evolution of a cytokine control mechanism."PNAS,1991,88(12):5232-5236)通过分子克隆技术分析IL-1Ra的基因长1.8kb，有编码177个氨基酸的开放阅读框；成熟的IL-1Ra蛋白有152个氨基酸，还有一个25个氨基酸的先导序列。其与IL-1β有26％～30％同源性，与IL-1α有19％同源性，基因结构与IL-1相似。因此，可以推测IL-1Ra与IL-1结构相似的部分起到与受体结合的作用，但它不能引发跨膜转导信号。在疾病状态下，许多组织如滑膜、皮肤组织中的巨噬细胞都可产生IL-1Ra。人的正常皮肤、培养的角质细胞及单核细胞皆有IL-1Ra mRNA表达。IL-1Ra与IL-1受体结合后，本身无激动作用，但可消除或减轻IL-1的生物效应，从而影响机体的病理生理过程。IL-1和IL-1Ra之间的平衡决定IL-1在炎症过程中的作用。

[0008] 大量实验证明，IL-1Ra具有抑制前列腺素生成、引起血清NO浓度、减低环氧合酶-2和胶原酶-1的表达量、阻止白细胞浸润及关节软骨蛋白聚糖的降解、拮抗IL-1β的促神经生长因子表达等功能，预示IL-1Ra在治疗类风湿性关节炎、淀粉样变性病、骨关节炎、过敏性脑脊髓炎等炎症疾病中有着广阔的应用前景。IL-1Ra也可改善肾炎、皮炎及呼吸道炎症，降低脓毒休克死亡率，提高热休克存活率，抑制骨髓瘤生长，提高角膜同种移植成功率。一些诱导IL-1Ra表达的物质，其中包括人血清IgA、皮质类固醇、非类固醇抗炎药物mofezolac、IL-4、IL-13、IFN、TGF-β、IL-6及其它经gp130转导信号的细胞因子，同样可用于治疗IL-1所致疾病。

[0009] IL-1Ra商品名为Kineret。Kineret(Anakinra，阿那白滞素)是一种重组的非糖基化的人IL-1Ra(rhIL-1Ra)，由153个氨基酸组成，分子量为17.3KD，由美国Amgen公司开发。Kineret与天然的人IL-1Ra的区别在于它的氨基端增加了一个蛋氨酸残基。2001年11月14日，Kineret获得美国FDA的批准上市，用于治疗对一种或多种DMARD无效的中至重度的活动期成人类风湿性关节炎患者，以减轻其症状。欧洲专利药评估署于2001年11月21日批准Kineret在欧洲上市，与MTX联用治疗对单用MTX疗效欠佳类风湿性关节炎患者。目前，Kineret正在进行用于炎症性肠病(IBD)、气喘和移植物排异的临床试验。

[0010] 糖尿病的发生与胰岛β细胞功能受损有关，随着患病时间的延长，胰岛β细胞功能将进行性衰退。目前已经发现，在由胰岛β细胞炎症引发β细胞破坏和功能损伤而导致的1型糖尿病中，前炎症因子IL-1β在抑制胰岛β细胞功能和促其凋亡的过程中发挥了重要作用。在2型糖尿病患者中，也观察到胰岛β细胞IL-1表达增强，同时IL-1Ra的表达减弱。IL-1Ra的不足似乎是遗传特性，因为编码IL-1Ra的基因其基因多态性和改变的血清IL-1Ra含量是相关联的。IL-1β可以促进胰岛炎症细胞因子表达，并增加免疫细胞的浸润从而引发组织炎症，并影响β细胞功能和胰岛素敏感性。在体外研究中，长期暴露于高浓度葡萄糖和由脂肪组织分泌的肽激素瘦素会诱使β细胞及胰岛产生并释放IL-1β，继而引起功能受损及β细胞凋亡。外源性添加IL-1受体拮抗剂，如IL-1Ra，可以保护β细胞免受高浓度葡萄糖和瘦素的

损伤,并减少2型糖尿病患者的炎症标识。类似研究也证实,胰岛内生成的炎性介质与糖尿病密切相关(Böni-Schnetzler等,“Increased Interleukin(IL)-1βMessenger Ribonucleic Acid Expression inβ-Cells of Individuals with Type 2Diabetes and Regulation of IL-1βin Human Islets by Glucose and Autostimulation.”J Clin Endocrinol Metab,2008,93(10):4065-4074;Donath等,“Islet Inflammation Impairs the Pancreatic {beta}-Cell in Type 2Diabetes.”Physiology(Bethesda).2009,24:325-331)。

[0011] 在一项研究中(Ehses等,“IL-1antagonism reduces hyperglycemia and tissue inflammation in the type 2diabetic GK rat”,PNAS,2009,106(33):13998-14003),研究者着重探讨IL-1对胰岛炎症细胞因子产生以及对胰岛素作用的周围组织炎症的影响。研究者选择GK大鼠为研究对象。该大鼠是一种自发性非肥胖的2型糖尿病模型大鼠,会发生胰岛的炎症和周围组织的(肝脏、骨骼肌和脂肪组织)胰岛素抵抗。研究者发现,GK大鼠胰岛和肝脏组织大量表达IL-1β,体外给予大鼠IL-1Ra可以特异性阻断IL-1活性,降低胰岛炎症细胞因子的释放。体内试验也证实IL-1Ra可以改善GK大鼠的高血糖,改善β细胞功能和胰岛素抵抗。此外,IL-1Ra可以降低胰岛来源的前炎细胞因子如IL-1β、IL-6、TNFα、KC、MCP-1和MIP-1α水平并减少胰岛CD68+、MHC II+和CD53+免疫细胞的浸润。肝脏组织细胞因子表达也减少。因此,IL-1Ra能够改善β细胞功能,有可能治疗2型糖尿病。

[0012] 瑞士苏黎世大学MarcY.Donath等人利用阿那白滞素进行了一项临床双盲试验,结果发现,阻断IL-1可以改善患者的高血糖及胰岛β细胞功能,同时降低血液中炎性标志物的水平。此外,Marc Y.Donath等人还利用抗IL-1抗体XOMA 052进行临床双盲试验,以了解其安全性和药代动力学,试验中患者对该药有很好的耐受性,未发现药物相关的严重不良反应。

[0013] 在一个研究中,70名A_1C>7.5%且BMI>27kg/m^2的2型糖尿病患者被随机安排接受为期13周的阿那白滞素或安慰剂治疗。在撤销阿那白滞素39周后,与安慰剂组病人的数据对比,发现通过阿那白滞素阻滞IL-1可以带来PI/I比值及系统性炎症标识的改善,而这一改善在治疗撤除之后依然可以持续39周(Larsen等,“Sustained Effects of Interleukin-1 Receptor Antagonist Treatment in Type 2Diabetes”,Diabetes Care 2009,32:1663-1668)。

[0014] 综上所述,炎症因子是糖尿病发生的重要因素之一。除目前的传统治疗外,抗炎治疗可能成为治疗糖尿病的新途径。

[0015] 由于微量的IL-1就可以引起完全的生物学效应,IL-1ra的浓度往往需要高于IL-1 100倍以上才能有效地抑制IL-1的生物学效应。在类风湿性关节炎治疗过程中,阿那白滞素的用量高达100～150mg/d,因而对生物制药下游工艺和生产有很高的要求,对生物制药企业是一个挑战。IL-1Ra理论上可以作用于体内任何部位的IL-1受体,没有选择性。长期、大剂量使用是否会使病人因为免疫抑制导致感染增加也是一个疑问;尤其是糖尿病人本身就容易受到感染,而且不易治愈。频繁用药加重了病人的身体、心理和经济负担。另外,IL-1Ra在体内半衰期只有4-6小时,消弱了效果,增加了使用剂量。因此,设计新型靶向性IL-1ra,改善糖尿病治疗效果,减少不必要免疫抑制,降低剂量,延长体内作用时间是新药开发的方向。

发明内容

[0016] 本发明的目的是提供一种新的糖尿病治疗药物，所述药物包括一种融合蛋白或其缀合物。

[0017] 在一个方面，本发明提供一种融合蛋白，所述融合蛋白由两种多肽通过连接而构成，其中一种多肽是白介素-1受体拮抗蛋白或其类似物，另一种多肽是GLP-1受体结合多肽或其类似物、或GIP受体结合多肽或其类似物、或胰岛素受体结合多肽或其类似物；

[0018] 所述融合蛋白的结构为：白介素-1受体拮抗蛋白或其类似物-L_j-另一种多肽，或者另一种多肽-Lj-白介素-1受体拮抗蛋白或其类似物；

[0019] 所述白介素-1受体拮抗蛋白或其类似物的序列是：

[0020] X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE，其中，

[0021] X_{IL0}是甲硫氨酸、半胱氨酸、通式1、通式2或缺失；

[0022] X_{IL66}、X_{IL69}、X_{IL116}、X_{IL122}是半胱氨酸或丝氨酸；X_{IL84}是半胱氨酸或天冬酰胺；

[0023] L_j是连接基或间隔基，包括长链脂肪酸、聚乙二醇、氨基酸、短肽、蛋白，或一个或多个可选的长链脂肪酸、聚乙二醇、氨基酸、短肽等通过共价键连接而成的长链，或任何将两个蛋白/多肽通过共价键连接的结构，或缺失；优选地，所述连接基或间隔基含有一个或一个以上的赖氨酸或半胱氨酸，其侧链的氨基或巯基可用于与修饰基团反应；优选地，所述短肽的通式是$(GlyGlyGlyGlySer)_n$，n是0、1、2、3、4、5或6。

[0024] 在一个方面，本发明提供一种蛋白缀合物，所述蛋白缀合物是在本发明的融合蛋白基础上进行酰化、接枝等修饰而获得的化合物。

[0025] 在一个方面，本发明提供一种药物组合物，包括本发明的融合蛋白或蛋白缀合物和制药学上可接受的载体或添加剂。

[0026] 在一个方面，本发明提供所述的融合蛋白、蛋白缀合物或药物组合物在治疗糖尿病中的应用。

[0027] 在一个方面，本发明提供所述的融合蛋白、蛋白缀合物在制备治疗糖尿病的药物中的应用。

[0028] 在一个方面，本发明提供一种治疗糖尿病的方法，所述方法包括对需要的病患施用本发明的融合蛋白、蛋白缀合物或药物组合物。

[0029] 本发明的融合蛋白及其衍生物具有明显的治疗糖尿病的功效，且用量少，对使用者的副作用明显降低。

附图说明

[0030] 图1A和图1B分别是天然白介素-1受体拮抗蛋白(IL-1Ra)(图中IL-1ra-40-SUMO)和G-20(图中IL-1ra-SUMO)表达载体结构。

[0031] 图2是天然白介素-1受体拮抗蛋白(IL-1Ra)(图中IL-1ra-40)和G-20(图中IL-1ra)DNA测序结果。

[0032] 图3A-3C是用亲合色谱法初步纯化带有SUMO标签的融合蛋白G-20的电泳图，其中，

[0033] 图3A第一泳道是蛋白分子量标准，从最下起分别为9K，14K，22K，30K，41K；第二甬

道为细胞裂解液，第三泳道为过柱洗涤缓冲液，第四泳道是过柱洗脱缓冲液；

[0034] 图3B第一和第二泳道分别是经过2次纯化的带有SUMO标签的融合蛋白G-20；第三泳道是蛋白分子量标准；

[0035] 图3C第一泳道是蛋白分子量标准，第二泳道是切除SUMO标签后的融合蛋白G-20。

[0036] 图4是以RP-HPLC和特殊缓冲液梯度分析融合蛋白G-20样品纯度。

[0037] 图5是融合蛋白G-20的质谱图。

[0038] 图6A和图6B是用本发明中的蛋白表达方法制备的天然白介素-1受体拮抗剂的肽质量指纹谱，该蛋白用于动物试验中的对照。

[0039] 图7是动物试验的血糖检测结果。四组小鼠分别接受生理盐水、白介素-1受体拮抗剂、融合蛋白G2和G-20(两个代表性GLP-1受体结合多肽-连接基-白介素-1受体拮抗蛋白融合蛋白)治疗12周后，在糖耐量试验中的血糖变化。

[0040] 图8是动物试验中胰岛素水平检测结果。四组小鼠分别接受生理盐水(图中1)、白介素-1受体拮抗剂(图中2)、G-20(图中3)和G-2(图中4)(两个代表性GLP-1受体结合多肽-连接基-白介素-1受体拮抗蛋白融合蛋白)治疗12周后，在糖耐量试验中的胰岛素水平的变化。

[0041] 图9是动物试验的血糖检测结果。四组小鼠分别接受生理盐水、白介素-1受体拮抗剂、融合蛋白IN-7和IN-62(两个代表性胰岛素受体结合多肽-连接基-白介素-1受体拮抗蛋白融合蛋白)治疗12周后，在胰岛素耐量试验中的血糖变化。

[0042] 图10是动物试验的血糖检测结果。四组小鼠分别接受生理盐水、白介素-1受体拮抗剂、融合蛋白GI-3和GI-7(两个代表性GIP受体结合多肽-连接基-白介素-1受体拮抗蛋白融合蛋白)治疗12周后，在糖耐量试验中的血糖变化。

具体实施方式

[0043] 定义及术语

[0044] 除非另外说明，下述定义适用于本发明全文。未定义的术语可以根据行业内约定俗成的定义理解。

[0045] 本申请中，hIL-1Ra或IL-1Ra表示成熟人白细胞介素-1受体拮抗剂；IL-1ra表示其类似物，包括本发明提供的白细胞介素-1受体拮抗剂及其缀合物。

[0046] “氨基酸”指任何同时包含氨基和羧基官能团的分子，α-氨基酸的氨基和羧基连接在同一个碳原子上(α碳)。α碳可以有1-2个有机取代基。氨基酸包含L和D同分异构体和消旋混合物。如无特别说明，本发明中多肽序列中的氨基酸残基都是L同分异构体即L-氨基酸，D-氨基酸在氨基酸名称或缩写前加小写字母“d”表示，如dK。

[0047] “可编码的氨基酸”或“可编码的氨基酸残基”用于表示可以由核苷酸三联体编码的氨基酸或氨基酸残基，其中，

[0048] hGlu为高谷氨酸；

[0049] α-hGlu为-HNCH(CO-)$CH_2CH_2CH_2COOH$的L同分异构体；

[0050] δ-hGlu为-HNCH(COOH)$CH_2CH_2CH_2CO$-的L同分异构体；

[0051] α-Asp为-HNCH(CO-)CH_2COOH的L同分异构体；

[0052] β-Asp为-HNCH(COOH)CH_2CO-的L同分异构体；

[0053] α-Glu为-HNCH(CO-)CH_2CH_2COOH的L同分异构体；

[0054] γ-Glu为-HNCH(COOH)CH_2CH_2CO-的L同分异构体；

[0055] β-Ala为-HN-CH_2-CH_2-COOH；

[0056] Sar为肌氨酸。

[0057] 氨基酸残基可以用三字母氨基酸编码或者单字母氨基酸编码表示；氨基酸表如下：

[0058] 表一：氨基酸名称及简写

[0059]

中文名称	英文名称	三字母	单字母	中文名称	英文名称	三字母	单字母
甘氨酸	Glycine	Gly	G	苏氨酸	Threonine	Thr	T
丙氨酸	Alanine	Ala	A	半胱氨酸	Cysteine	Cys	C
缬氨酸	Valine	Val	V	甲硫氨酸	Methionine	Met	M
亮氨酸	Leucine	Leu	L	天冬酰胺	Asparagine	Asn	N

[0060]

异亮氨酸	Isoleucine	Ile	I	谷氨酰胺	Glutamine	Gln	Q
脯氨酸	Proline	Pro	P	色氨酸	Tryptophan	Trp	W
苯丙氨酸	Phenylalanine	Phe	F	丝氨酸	Serine	Ser	S
酪氨酸	Tyrosine	Tyr	Y	赖氨酸	Lysine	Lys	K
天冬氨酸	Aspartic acid	Asp	D	精氨酸	Arginine	Arg	R
谷氨酸	Glutamic acid	Glu	E	组氨酸	Histidine	His	H

[0061] 胰岛素相关内容：

[0062] “天然胰岛素”指来源于天然、化学合成、基因工程生产的哺乳动物胰岛素(如人胰岛素、牛胰岛素、猪胰岛素等)。人胰岛素包含21个氨基酸组成的A链和30个氨基酸组成的B链。两条链通过3条二硫键相连：A7和B7、A20和B19、A6和A11。B7、A7指的是天然人胰岛素B链位置7(从N端数起)的氨基酸残基以及胰岛素A链位置7(从N端数起)的氨基酸残基，同理类推其它位置。

[0063] “胰岛素类似物”是修改过的胰岛素多肽的通称，包括与天然胰岛素有同源序列的由A链和B链组成的双链分子，以及单链胰岛素类似物。“胰岛素类似物”具有天然胰岛素的部分、全部或增强活性，或者在体内或体外能够转化为具有天然胰岛素的部分、全部或增强活性的多肽，例如比天然胰岛素增加、减少或替换一个或多个氨基酸残基的多肽。人、动物乃至非哺乳动物的胰岛素原、前胰岛素原、胰岛素前体、单链胰岛素前体和类似物都称为“胰岛素类似物”。很多胰岛素类似物见诸于文献。除非特别另外说明，本文中“胰岛素类似物”广义包括天然胰岛素和胰岛素类似物。

[0064] “胰岛素受体结合多肽”包括胰岛素类似物、衍生物及其缀合物，和其它与胰岛素受体有结合能力的多肽，如胰岛素样生长因子-1(IGF-1)和胰岛素样生长因子-2(IGF-2)及其类似物、衍生物和缀合物。

[0065] 如无特殊说明，本申请中以A链或B链位置说明的氨基酸，如A14、B28等都表示与胰岛素的A链或B链相对应位置的氨基酸残基或其变化形式，其中胰岛素的A链或B链的编号从N末端的第一位开始计算。

[0066] 单独指某一个氨基酸残基时，可以用例如A1G、B1G或B9H表示，其分别指在A链的第一个氨基酸、B链的第一个和第九个氨基酸残基分别是G、G、H。

[0067] 单链胰岛素化合物的编号按照各化合物的说明为准。

[0068] 单链胰岛素化合物指的是具有一般结构B链-C_L-A链的多肽序列或修饰的多肽序列，其中B链是胰岛素的B链或类似物，A链是胰岛素的A链或类似物，C_L是连接B链C末端氨基酸残基与A链N末端的肽链。

[0069] GLP-1、GLP-1类似物及GLP-1受体结合多肽：

[0070] 胰高血糖素原包含有两种胰高血糖素样肽，即GLP-1和GLP-2。GLP-1主要由末端空肠、回肠和结肠的Langerhans细胞分泌，主要包括GLP-1(7-37)和GLP-1(7-36)-NH_2两种形式。GLP-1(7-36)-NH_2是人体内的GLP-1的自然存在形式，在GLP-1肽中，它的促进胰岛素分泌作用最强。

[0071] GLP-1(7-36)-NH_2序列为：

[0072] HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR-NH_2；

[0073] GLP-1(7-37)序列为：

[0074] HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG。

[0075] GLP-1在体内的表达和活性受到严密的调控。当N端第二位丙氨酸被二肽基肽酶(DPP-Ⅳ)水解后，形成无活性的GLP-1(9-36)-NH_2，成为GLP-1R的体内天然拮抗剂。在体内，GLP-1经酶切后的几个代谢产物包括GLP-1(9-36)、GLP-1(7-35)和GLP-1(7-34)。GLP-1(9-36)-NH_2是GLP-1的主要分解代谢产物，在体内的浓度可以高达GLP-1(7-36)-NH_2的10倍。GLP-1在体内的半衰期不足5分钟，其新陈代谢的速率为12～13分钟。在生理状态下，完整的GLP-1主要是通过肾脏的排泄，由肾外组织协助排除。

[0076] GLP-1能够促进胰岛素分泌，而且这种促进作用是葡萄糖依赖性的，血糖越高，作用越强。GLP-1与胰岛β细胞细胞膜上的受体结合，通过增加细胞内cAMP，使K^+-ATP酶磷酸化，导致K^+通道关闭，细胞膜去极化，Ca^{2+}通道开放，Ca^{2+}内流，刺激胰岛素从细胞排出，从而促进胰岛素分泌。这种作用又是全方位的，影响前胰岛素基因的转录、翻译及剪切等各个功能环节。此外，GLP-1也能够上调β细胞中与糖代谢密切相关的基因(如葡萄糖激酶和葡萄糖转运蛋白-2)，但胰岛素基因启动子可以部分不依赖PKA的方式被激活。

[0077] GLP-1也能够刺激胰岛β细胞增生，抑制其凋亡。研究发现GLP-1在非-STZ模型大鼠中能刺激β细胞新生，改善成年大鼠血糖的自身稳定。在新生GK大鼠中，经GLP-1或Exendin-4注射5日，血糖恒定状态显著改善，胰岛素水平升高，β细胞实体增大。继续应用上述药物，大鼠β细胞持续增加，成年时血糖控制能力显著提高。体外细胞培养发现，GLP-1能诱导小鼠成肌细胞株和胚胎干细胞分化为胰岛素表达细胞。在Zucker糖尿病大鼠模型中，β细胞凋亡的比例最高达20％以上，GLP-1的治疗能使凋亡细胞比例显著下降。研究发现，GLP-1能抑制链脲佐菌素(STZ)诱导的小鼠β细胞凋亡，而GLP-1R基因敲除小鼠的β细胞对STZ诱导凋亡的敏感性显著升高。

[0078] 在血糖调节中，胰升糖素的作用和胰岛素相反，通过促进肝糖原分解增加血糖的浓度。在健康人、1型糖尿病和2型糖尿病患者中均证实，GLP-1能抑制胰升糖素的释放，但在健康人体中其作用程度小于糖尿病患者。给C肽阴性的狗注射GLP-1能降低血浆胰高血糖素水平，提示GLP-1抑制胰高血糖素的作用至少部分是不依赖于胰岛素的。

[0079] 在对鼠、猪和人的一系列研究中发现，GLP-1可抑制胃肠道蠕动和胃液分泌，延迟胃排空。在人体，无论是正常人还是糖尿病患者，应用GLP-1均可使其产生短暂的饱胀感觉

和食欲下降。

[0080] GLP-1受体(GLP-1R)是一个与G蛋白偶联的7个跨膜结构,以cAMP为主要第二信使。它属于G蛋白偶联受体B家族(分泌素家族)中的胰高血糖素受体亚家族,该家族最明显的特征是相对较长的胞外N端序列,通过3个二硫键形成一个球状结构域。人GLP-1受体与鼠受体有90%的同源性。解剖学的证据表明:鼠、猪和人肠道各段都可见GLP-1R细胞,不同种属间分布密度不同,分布规律相同,即从小肠和大肠的近端向远端细胞逐渐增大。

[0081] 胰高血糖素原72-117的氨基酸序列参照Bell等,Nature 304 368-371(1983)。胰高血糖素原片段72-108通常称为GLP-1(1-37)。GLP-1(7-20)是已知的最短的促胰岛素的GLP-1类似物。

[0082] "GLP-1类似物"定义为GLP-1(1-37)的一个或多个氨基酸残基缺失或被另外的氨基酸残基取代,或者有一个或多个氨基酸残基插入原多肽序列。在一个优选的实施方式中,GLP-1类似物和对应的GLP-1(1-37)的不同氨基酸残基总数不超过20个,或不超过15个、10个、5个、4个、3个、2个,最好是1个。GLP-1类似物可以是GLP-1(1-37)的截断片段。GLP-1类似物也可以是GLP-1的N末端或C末端延伸后得到的序列。在某些实施方式中,GLP-1类似物包括C末端1-20个氨基酸的延长。在一种实施方式中,C末端的延伸序列是PSSGAPPPS-NH_2或GPSSGAPPPS-NH_2。在一种实施方式中,C末端延长包括1-6个带正电荷的氨基酸,如精氨酸、赖氨酸。在一种实施方式中,C末端延长包括1-6个带负电荷的氨基酸,如谷氨酸、天冬氨酸。在某些实施方式中,GLP-1类似物可以是修饰产物,例如烷基取代、酰化、聚乙二醇修饰等。

[0083] 不同的GLP-1有不同的生物活性。GLP-1(7-36)-NH_2刺激[^{14}C]-氨基比林蓄积的能力是GLP-1(1-37)和GLP-1(1-36)-NH_2的100倍;GLP-1(7-36)-NH_2和GLP-1(7-37)-NH_2有相当的活性和效果。GLP-1(9-36)-NH_2对β细胞没有效果,在某些研究中甚至是腺苷酸环化酶的拮抗剂;而GLP-1(7-35)-OH和GLP-1(7-34)-OH明显是激动剂。GLP-1(7-35)-OH或GLP-1(7-37)-OH升高血浆中胰岛素水平的能力低于GLP-1(7-36)-NH_2。

[0084] GLP-1(7-36)-NH_2与受体结合的部分主要是氨基酸残基7-21,尽管全长序列都可以在受体结合中起到协同作用。除氨基酸长链的骨架之外,序列第7(组氨酸)、10(甘氨酸)、12(苯丙氨酸)、13(苏氨酸)和15(天冬氨酸)的侧链都直接与受体作用。而序列第28(苯丙氨酸)和第29(异亮氨酸)对GLP-1形成能够被受体识别的构象很关键。有些研究表明序列第10(甘氨酸)、15(天冬氨酸)和17(丝氨酸)的氨基酸残基以及C末端对于GLP-1的促胰岛素作用很重要。C末端酰胺化和C末端最后的氨基酸残基对GLP-1作用的重要性不如N末端。

[0085] GLP-1受体拮抗剂主要来源于GLP-1(7-36)-NH_2或exendin-4的N端删除或取代后的序列,包括但不局限于以下序列:

[0086] 1.DLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2;

[0087] 2.HAKGTFTSDVSSYLEGQAAKEFIAWLVKGR-NH_2;

[0088] 3.EGTFTSDVSSYLEGQAAKEFIAWLVKGR-NH_2;

[0089] 4.AEGTFTSEVSSYLEGQAAKEFIAWLVKGR-NH_2。

[0090] GLP-1类似物包括那些与GLP-1(7-37)序列有1-15个氨基酸残基差异的多肽,包括11、12、16、22、23、24、25、26、27、30、33、34、35、36、37位的取代或修改。这些多肽的18、20、23、30、31、34、36、37位或C末端可以连接白蛋白结合分子或聚乙二醇等修饰基团(WO2009030738)。GLP-1受体结合多肽包括任何与GLP-1受体结合能力达到GLP-1(7-36)-

NH_2的1％、5％、10％、20％、30％、40％、50％、60％、70％、80％、90％、100％或超过100％的多肽及其衍生物，例如GLP-1类似物、GLP-1受体激动剂、GLP-1受体拮抗剂、GLP-1和胰高血糖素受体双激动剂(coagonist)、GLP-1受体激动剂和胰高血糖素受体拮抗剂嵌合多肽、胰高血糖素受体拮抗剂以及这些多肽的衍生物，包括出版物和文献中的序列，例如US7235627，WO/2002/048192，WO/2004/093823，WO/2003/103572，WO/2008/101017，WO/2009/058734，WO/2009/155258，WO/2010/070253，WO/2010/070255，WO/2011/075393，WO/2011/080102，WO/2011/073328，EP2322545，EP 2322546，“Design of a Long Acting Peptide Functioning as Both a Glucagon-like Peptide-1Receptor Agonist and a Glucagon Receptor Antagonist，”The Journal of Biologial Chemistry 2006，Vol.281(18):12506-12515。

[0091] 随着对GLP-1及其与糖尿病的相关性研究的不断深入，国内外医药研发机构越来越重视这一领域。代表性药物是Exendin-4和liraglutide。

[0092] Liraglutide与内源性人GLP-1(7-37)氨基酸序列有97％的相似度，序列为：

[0093] HAEGTFTSDVSSYLEGQAAK(γE-C16)EFIAWLVRGRG-OH。

[0094] 其它GLP-1类候选药物包括albiglutide、taspoglutide、lixisenatide(AVE0010或者ZP10A)等。

[0095] Albiglutide是融合在人白蛋白上的抗DPP-Ⅳ水解的GLP-1二聚物，半衰期为4-7天。

[0096] Lixisenatide序列为：

[0097] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPSKKKKKK-NH_2。

[0098] Taspoglutide是人GLP-1(7-36)的(2-甲基丙氨酸)-35-(2-甲基丙氨酸)-36-L精氨酸酰胺衍生物，序列为HAibEGTFTSDVSSYLEGQAAKEFIAWLVKAibR-NH_2。

[0099] 艾塞那肽(Exenatide)是Exendin-4的合成产物，由39个氨基酸组成，与GLP-1相似性高达53％，并且具有相同的生物学功能。艾塞那肽序列为：

[0100] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2。

[0101] Exendin-3是从Heloderma horridum的分泌产物中得到的，序列为

[0102] HSDGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2。

[0103] “Exendin-3类似物”定义为exendin-3的一个或多个氨基酸残基缺失或被另外的氨基酸残基取代，或者有一个或多个氨基酸残基插入原多肽序列。Exendin-3类似物包括那些与exendin-3序列有1-15个氨基酸残基差异的多肽。

[0104] “Exendin-4类似物”定义为exendin-4的一个或多个氨基酸残基缺失或被另外的氨基酸残基取代，或者有一个或多个氨基酸残基插入原多肽序列。在一种优选的实施方式中，exendin-4类似物和exendin-4的不同氨基酸残基总数可以是不超过15个、10个、5个、4个、3个、2个，最好是1个，例如亮氨酸14，苯丙氨酸25-exendin-4。Exendin-4类似物可以是exendin-4的截断片段，例如exendin-4(1-28)-NH_2、exendin-4(1-30)、exendin-4(1-30)-NH_2、亮氨酸14、苯丙氨酸25-exendin-4(1-28)-NH_2、亮氨酸14、丙氨酸22、苯丙氨酸25-exendin-4(1-28)-NH_2。

[0105] 本发明包括exendin-3和exendin-4的全长或截断序列，包括exendin-3(1-30)或exendin-4(1-30)序列，其中这些序列的C末端可缩短3个氨基酸残基，优选缩短1个氨基酸

残基;N末端可缩短2个氨基酸残基,优选缩短1个氨基酸。尽管氨基酸序列缩短了,但这些exendin片段都具有生物活性。

[0106] 本发明包括exendin-3和exendin-4的C末端延伸序列。在一个实施方式中,C末端延伸包括1-6个带正电荷的氨基酸,如精氨酸、赖氨酸。在一个实施方式中,C末端延伸包括1-6个带负电荷的氨基酸,如谷氨酸、天冬氨酸。在某些实施方式中,exendin-3和exendin-4类似物可以是修饰产物,例如烷基取代、酰化、聚乙二醇修饰等。

[0107] 以exendin-3和exendin-4为模板的GLP-1受体结合多肽包括任何与GLP-1受体结合能力达到GLP-1(7-36)-NH_2的1%、5%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%或超过100%的多肽及其衍生物,包括出版物和专利文献中的序列,例如在WO97/46584、WO 98/05351、WO 99/25727、WO 99/25728、WO 99/07404、WO 99/40788、WO 00/41546、WO 00/41548、US 7691963B2、US 7407932B2、US8030273B2、US20010047084A1、US 5424286A、WO/2013/002580、CN200710138718.7、CN200910135363.5、"EW,a novel recombinant analogue of exendin-4expressed in Escherichia coli"Scientific Research and Essays 2011Vol.6(14):2941-2949、"Site-specific PEGylation of exenatide analogues markedly improved their glucoregulatory activity"British Journal of Pharmacology,2011,163:399-412中提及的序列。

[0108] GIP及GIP受体结合多肽

[0109] 胃泌素抑制肽又称葡萄糖依赖性促胰岛素分泌多肽,简称GIP。当血糖浓度高时,GIP可以通过促进胰岛素分泌调节血糖。另外,GIP在脂肪细胞和脂肪代谢过程中起到重要作用。

[0110] 人GIP序列:YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQ。

[0111] "GIP类似物"定义为GIP的一个或多个氨基酸残基缺失或被另外的氨基酸残基取代,或者有一个或多个氨基酸残基插入原多肽序列。在一种实施方式中,GIP类似物与人GIP的序列至少有25%、30%、40%、50%、60%、70%、80%、90%相同。在一种优选的实施方式中,GIP类似物和人GIP的不同氨基酸残基总数可以是不超过20个、15个、10个、5个、4个、3个、2个,最好是1个。在某些实施方式中,氨基酸取代可以是第1、2、3、7、10、12、15、16、17、18、19、20、21、23、24、27、28和29位。GIP类似物可以是GIP(1-42)的截断片段。在一个实施方式中,GIP类似物包括GIP(1-42)从C末端去除1-12个氨基酸残基后的序列,例如GIP(1-38)、GIP(1-39)、GIP(1-30)-NH_2等。在一种实施方式中,GIP类似物包括GIP(1-42)从N末端起至少12个氨基酸残基的多肽序列。在某些实施方式中,GIP类似物包括C末端1-20个氨基酸的延长。在一种实施方式中,C末端延长包括1-6个带正电荷的氨基酸,如精氨酸、赖氨酸。在一种实施方式中,C末端延长包括1-6个带负电荷的氨基酸,如谷氨酸、天冬氨酸。在某些实施方式中,GIP类似物可以是修饰产物,例如烷基取代、酰化、聚乙二醇修饰等。

[0112] GIP类似物及其衍生物可以见于多种文献。部分GIP激动剂可见于出版物,例如Salhanick等,Bioorg Med Chem Lett 2005,15(18):4114-4117;Green等,Diabetes 2005,7(5):595-604;Gault等,Biochem J 2002,367(Pt3):913-920;Gault等,J Endocrin 2003;176:133-141;Irwin等,Diabetes Obes Metab 11(6):603-610(epub 2009)等。其它GIP类似物的例子有N-AcGIP(LysPAL^{37})(Irwin等"A Novel,Long-Acting Agonist of Glucose-Dependent Insulinotropic Polypeptide Suitable for Once-Daily Administration

in Type 2 Diabetes",J Pharmacol Exp Ther,2005vol.314no.3 1187-1194)、GIP(1-40)、GIP(1-30)-NH_2、GIP(19-30)-NH_2、GIP(1-14)(Hinke等,"Identification of a bioactive domain in the amino-terminus of glucose-dependent insulinotropic polypeptide(GIP)",Biochimica et Biophysica Acta 2001,Vol.1547 143-155)。由于GIP的C末端片段有较强的促进脂肪生成能力,因此部分或全部去掉C末端是降低GIP激动剂在这方面作用的方法之一,例如GIP(1-30)-NH_2。构效关系研究表明,GIP的19-30片段是胰岛素反应的关键("The insulinotropic region of gastric inhibitory polypeptide; fragment analysis suggests the bioactive site lies between residues 19and 30."Can J Physiol Pharmacol.1996Jan;74(1):65-72)。

[0113] GIP活性的一个重要决定因素是多肽N-端被DPP-4酶水解为没有活性的GIP(3-42)。对GIP N末端端第1、2或3位的适当修饰,可以抵抗DPP-4的降解,甚至使GIP类似物的生物活性提高。与天然GIP相比,[D-Ala2]-GIP(1-42)在正常小鼠体内GIP受体是超级激动剂,而且这种超常活性与其对血液胰岛素的效果并不完全相关("Dipeptidyl Peptidase IV-Resistant[D-Ala2]Glucose-Dependent Insulinotropic Polypeptide(GIP)Improves Glucose Tolerance in Normal and Obese Diabetic Rats",Diabetes 2002 51:652-661)。

[0114] 去除GIP的N末端氨基酸残基往往得到GIP受体拮抗剂。GIP(10-30)-NH_2、GIP(6-30)-NH_2和GIP(7-30)-NH_2是GIP受体拮抗剂,其中GIP(6-30)-NH_2与GIP受体的结合能力与GIP(1-42)相当(Gelling等,"GIP(6-30amide)contains the high affinity binding region of GIP and is a potent inhibitor of GIP1-42 action in vitro."Regul Pept.1997,69(3):151-154;"Postprandial stimulation of insulin release by glucose-dependent insulinotropic polypeptide (GIP).Effect of a specific glucose-dependent insulinotropic polypeptide receptor antagonist in the rat",J Clin Invest.1996December 1;98(11):2440-2445)。其它GIP拮抗剂包括GIP(15-42)、GIP(15-30)、GIP(16-30)、GIP(17-30)。GIP类似物Pro3-GIP("Characterization of the cellular and metabolic effects of a novel enzyme-resistant antagonist of glucose-dependent insulinotropic polypeptide."Biochem Biophys Res Commun.2002Feb 8;290(5):1420-6)体外在细胞中以及体内在糖尿病肥胖ob/ob小鼠中拮抗GIP作用("Effects of the novel(Pro(3))GIP antagonist and exendin(9-39)amide on GIP-and GLP-1-induced cyclic AMP generation,insulin secretion and postprandial insulin release in obese diabetic(ob/ob)mice:evidence that GIP is the major physiological incretin."Diabetologia.2003Feb;46(2):222-30;"Effects of the novel(Pro(3))GIP antagonist and exendin(9-39)amide on GIP-and GLP-1-induced cyclic AMP generation,insulin secretion and postprandial insulin release in obese diabetic(ob/ob)mice:evidence that GIP is the major physiological incretin.Diabetologia.2003Feb;46(2):222-30)。成年、高脂肪食物喂养的糖尿病小鼠连续50天注射Pro3-GIP后体重降低,脂肪组织堆积减少,葡萄糖、糖化血红蛋白、胰岛素水平显著改善,肌肉和肝脏的甘油三脂水平下降(McClean等,"GIPreceptor antagonism reverses obesity,insulin resistance and associated metabolic

disturbances induced in mice by prolonged consumption of high fat diet."Am J Physiol Endocrinol Metab.2007Dec;293(6):E1746-55)。

[0115] 2型糖尿病的特征包括不同程度的胰岛素抵抗和胰岛β细胞功能障碍。在欧洲和美国,胰岛素抵抗和肥胖是糖尿病患者的主要病理特证。在亚洲,胰岛素分泌能力受损是主要原因。因此,GIP激动剂可能对于胰岛素分泌能力受损的患者,尤其是亚洲患者有益,而GIP抑制剂可能对于胰岛素抵抗的肥胖患者,尤其是欧美患者有帮助。

[0116] 在某些实施方式中,与白介素-1受体结合多肽组成融合蛋白或二聚蛋白的是GIP激动剂、GIP抑制剂、GLP-1/GIP受体双激动剂、胰高血糖素/GIP受体双激动剂、GLP-1/GIP/胰高血糖素受体三激动剂(如WO/2010/011439、WO2010148089A1、US2012/0172295、US2011/0166062、US2012/0322725中提到的)、GLP-1激动剂/GIP抑制剂,或嵌合多肽(例如HG-GIP(3-30)-NH_2、HG-GIP(3-30)-exendin-4(31-39)-NH_2、Ser2-GIP(1-30)-NH_2、Ser2-GIP(1-30)-exendin-4(31-39)-NH_2、dAla2-GIP(1-30)-exendin-4(31-39)-NH_2)。在本发明中,GIP受体结合多肽可以是上述任何与GIP受体有结合能力的多肽序列。GIP受体结合多肽包括GIP类似物在内的任何与GIP受体有GIP(1-42)的0.1%、0.2%、0.3%、0.4%、0.5%、0.6%、0.7%、0.8%、0.9%、1%、5%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%或更高结合能力的多肽序列及其衍生物。

[0117] GIP在体外有刺激β细胞增殖、保护β细胞生存的效果("Glucose-Dependent Insulinotropic Polypeptide Is a Growth Factor for beta(INS-1)Cells by Pleiotropic Signaling."Mol Endocrinol.2001Sep;15(9):1559-70;"Mechanisms of mitogenic and anti-apoptotic signaling by glucose-dependent insulinotropic polypeptide in beta(INS-1)-cells",J Endocrinol.2002Aug,174(2):233-46;"Glucose-dependent insulinotropic polypeptide promotes beta-(INS-1)cell survival via cyclic adenosine monophosphate-mediated caspase-3inhibition and regulation of p38 mitogen-activated protein kinase",Endocrinology.2003Oct,144(10):4433-45)。多项研究表明GIP类似物在2型糖尿病大鼠模型和INS-1β细胞中有很强的生存保护能力("A GIP receptor agonist exhibits beta-cell anti-apoptotic actions in rat models of diabetes resulting in improved beta-cell function and glycemic control",PLoS One.2010Mar 9;5(3):e9590;"GIP stimulation of pancreatic beta-cell survival is dependent upon phosphatidylinositol 3-kinase(PI3-K)/protein kinase B(PKB)signaling,inactivation of the forkhead transcription factor Foxo1 and downregulation of bax expression.J Biol Chem.2005,280(23):22297-307)。

[0118] 由于GIP对胰岛β细胞的保护作用,GIP与白介素-1受体结合多肽组成融合蛋白、二聚蛋白或交联蛋白能够产生更好的效果。在本发明中,GIP受体结合多肽与白介素-1受体结合多肽的连接方式,可以参照GLP-1受体结合多肽与白介素-1受体结合多肽的连接方式。

[0119] 白介素-1受体拮抗蛋白:

[0120] "白介素-1受体拮抗蛋白"包括白介素-1受体拮抗剂(IL-1ra)及其类似物和衍生物。

[0121] IL-1受体家族包括几个受体,因此有几种不同的激动剂和拮抗剂。这些拮抗剂不

一定与相同的IL-1家族受体结合。这里IL-1ra用来代表所有IL-1受体家族受体的所有IL-1拮抗剂。IL-1ra包括人IL-1Ra(hIL-1Ra)及其类似物、衍生物或功能等同物。功能等同物具有hIL-1Ra的生物活性,例如可以结合IL-1受体,不产生下游信号传递,并阻止IL-1结合IL-1受体。例子可以参考美国专利号6096728、美国专利号6541623、美国专利号6365726和美国专利号6399573。

[0122] 优选的IL-1ra(包括糖基化和非糖基化的)的制备和使用方法的描述见美国专利号5,075,222、WO 91/08285、WO 91/17184、AU 9173636、WO 92/16221和WO 96/22793。具体而言,美国专利号5,075,222描述了3种形式的IL-1Ra。第一个IL-1Raα的特征是在SDS-PAGE上的分子量为22-23kD,等电点大约是4.8,用大约含52mM NaCl的Tris缓冲液(pH 7.6)从Mono Q FPLC柱洗脱。第二个是IL-1Raβ,是分子量22-23kD的蛋白,用含48mM NaCl的Tris缓冲液从Mono Q FPLC柱洗脱。IL-1Raα和IL-1Raβ都是糖基化的。第三个是IL-1Rax,分子量约20kD,用含有大约48mM NaCl的Tris缓冲液从Mono Q FPLC柱洗脱,无糖基化。这三种拮抗剂有类似的功能和免疫学活性。

[0123] 目前已知IL-1Ra包括一种分泌型亚型(sIL-1Ra)和三种细胞内亚型(icIL-1Ra1、2、3)。

[0124] 本发明所述的IL-1Ra可以是天然分泌型人IL-1Ra、基因重组型人IL-1Ra,优选是基因重组型人IL-1Ra。

[0125] 在有些实施方式中,IL-1ra包括阿那白滞素及其类似物。阿那白滞素的序列为:

[0126] MRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE。

[0127] 其中第70位和第117位的两个半胱氨酸可以形成二硫键。

[0128] 本发明中的IL-1ra及其类似物可以使用生物工程技术制备和生产。为了蛋白表达和生产的便利,甲硫氨酸可以根据需要添加到本发明中各蛋白序列的N末端,而不会影响原序列的生物活性。阿那白滞素即是在非糖基化hIL-1Ra的N末端加入甲硫氨酸。

[0129] 在有些实施方式中,IL-1ra包含一个或多个糖基化基团。

[0130] 本发明中IL-1ra的氨基酸序列可以改变而不影响其生物活性。例如,一个IL-1ra类似物可以包含一个或多个保守氨基酸取代。保守氨基酸取代是一个氨基酸残基被另一个有相似侧链的氨基酸残基取代。文献中根据氨基酸残基侧链的性质对氨基酸残基进行分类。碱性侧链氨基酸残基包括赖氨酸、精氨酸、组氨酸;酸性侧链及其酰胺侧链氨基酸残基包括天冬氨酸、谷氨酸、天冬酰胺、谷氨酰胺;小脂肪族、非极性或弱极性侧链氨基酸残基包括甘氨酸、丙氨酸、苏氨酸、丝氨酸、脯氨酸;大脂肪族、非极性侧链氨基酸残基包括亮氨酸、异亮氨酸、缬氨酸;芳香族氨基酸残基包括苯丙氨酸、色氨酸、酪氨酸;含硫侧链氨基酸残基包括半胱氨酸、甲硫氨酸。

[0131] 本发明中涉及的IL-1ra的类似物包括在IL-1ra的氨基酸序列中的部分氨基酸残基缺失(缺失类似物)、被其它天然或非天然氨基酸残基取代(取代类似物)或插入(插入类似物)。IL-1ra缺失类似物通常可以有大约1-50个氨基酸残基的缺失,更常见的是1-10个残基缺失。IL-1ra插入类似物可以包括在IL-1ra的N末端或C末端的融合,以及1个或多个氨基酸残基插入至IL-1ra的内部序列。IL-1ra的末端插入包括嵌合蛋白。在一种实施方式中,嵌

合蛋白包括IL-1ra与人免疫球蛋白重链或轻链的所有或部分恒定区。优选的嵌合蛋白的免疫球蛋白部分可以包含除人免疫球蛋白(如IgG,IgA,IgM或IgE)重链恒定区的第一个结构域外的所有恒定区。每个免疫球蛋白部分的任何氨基酸残基都可以缺失或用一个或多个氨基酸残基取代,或可以插入一个或多个氨基酸残基,只要所述IL-1ra仍然拮抗IL-1受体,而且所述免疫球蛋白部分表现出一个或多个其特征性质。IL-1ra末端的嵌合蛋白也可以包括部分或全部人白蛋白序列,白蛋白部分的任何氨基酸残基都可以缺失或用一个或多个氨基酸残基取代,或可以插入一个或多个氨基酸残基。

[0132] 本发明所述白介素-1受体拮抗蛋白类似物与IL-1Ra大致同源。本文所用的术语“大致同源”是指同源的程度超过60%、70%、80%、90%,甚至超过95%。本文所述同源百分比按Dayhoff(Atlas of Protein Sequence and Structure,5:124(1972),National Biochemical Research Foundation,Washington,D.C.)所述方法计算。

[0133] IL-1ra可以对白介素-1受体有hIL-1Ra的1%、2%、3%、4%、5%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%或更高的生物活性。

[0134] 本领域技术人员可以制备化学或生物修饰的IL-1ra及其类似物、衍生物。用糖基化、非糖基化或去糖基化IL-1ra和IL-1ra类似物可以制备缀合物,所用化学修饰基团包括水溶性聚合物(如聚乙二醇)和脂肪酸。一个IL-1ra类似物可以包含一个或多个修饰基团。化学修饰基团一般通过IL-1ra的氨基酸的α-或ε-氨基或活性硫羟基连接到IL-1ra。具有游离氨基的氨基酸残基包括赖氨酸残基和N末端的氨基酸残基。具有活性硫羟基的氨基酸残基包括半胱氨酸残基。

[0135] IL-1ra序列中的氨基酸残基特异性取代可以有特殊用途,比如加入半胱氨酸或赖氨酸对于按下述实施方法连接修饰基团以形成缀合物是有利的。此外,可以在IL-1ra的序列中加入或缺失N-连接或O-连接的糖基化位点。天冬酰胺连接的糖基化识别位点包括一个由适当的细胞糖基化酶识别的三肽序列Asn-Xaa-Ser/Thr,这里Xaa可以是Pro以外的任何天然氨基酸。在成熟的hIL-1Ra中,第84位的天冬酰胺是一个糖基化位点。根据糖基化程度的不同,糖基化IL-1ra的分子量可以不同。融合蛋白、二聚蛋白或交联蛋白中的白介素-1受体拮抗蛋白部分可以通过半胱氨酸侧链巯基与修饰基团(例如聚乙二醇)相连。

[0136] 成熟hIL-1Ra的氨基酸残基的编号依照以下氨基酸序列,N末端第一个氨基酸残基的位置为第一位,序列为:

[0137] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE。

[0138] 上述天然IL-1ra序列有4个半胱氨酸(C66、C69、C116、C122)。根据本发明中的实施方法,与马来酰亚胺或卤代乙酰基(例如I-CH_2-CO-)活化的修饰基团(例如单聚乙二醇)反应的IL-1ra特定位点为116位的半胱氨酸(C116)。在人IL-1ra中,其它3个半胱氨酸不易与马来酰亚胺或卤代乙酰基活化的修饰基团反应。为将修饰基团连接到IL-1ra的不同位点,或者使IL-1ra有一个以上的修饰基团,可以用半胱氨酸取代特定位点的氨基酸残基。IL-1ra类似物包括半胱氨酸添加到蛋白的N末端或C末端的序列,或用半胱氨酸取代原位点6、8、9、84或141的氨基酸残基的序列,或者116位的半胱氨酸被丝氨酸取代,或者4个半胱氨酸中一个或多个被丝氨酸取代。除单修饰基团的IL-1ra之外,IL-1ra还可以包括上述变化的

组合,从而有一个以上的半胱氨酸与修饰基团反应。

[0139] 相应的部分IL-1ra类似物序列如下:

[0140] CRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;

[0141] CRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;

[0142] CRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVCITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;

[0143] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVCITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;

[0144] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVCITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;

[0145] RPSGRCSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;

[0146] RPSGRCSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;

[0147] RPSGRKSCKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;

[0148] RPSGRKSCKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;

[0149] RPSGRKSSCMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;

[0150] RPSGRKSSCMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或

[0151] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGCMVTKFYFQEDE。

[0152] 这些IL-1ra类似物都可以用于合成本发明的融合蛋白、二聚蛋白或交联蛋白。

[0153] 修饰基团

[0154] 融合蛋白可以包含1个或多个修饰基团。修饰基团能够提供融合蛋白、二聚蛋白或交联蛋白需要的特性。例如，修饰基团可以降低蛋白在各种环境下(如消化道，血液)的降解速率。优选的修饰基团是那些允许蛋白保留相当的与原受体结合活性的基团。优选的修饰基团包括两性基团、水溶性基团或者使修饰后的蛋白比未修饰的蛋白更低亲脂性、更高水溶性的基团。修饰基团可以包含可降解连接基、易于水解的连接基，如丙交酯、乙交酯、碳酸、酯、氨基甲酸酯。这种方法可以使聚合物降解成小分子量片段。

[0155] 修饰基团可以包括一个或多个亲水基团、亲脂基团、两性基团、成盐基团、间隔基团、连接基团、封端基团或这些基团的组合。各种基团可以以共价键，或以可水解或不可水解的键连接在一起。代表性亲水基团、亲脂基团和两性基团介绍如下。

[0156] 亲水基团

[0157] 亲水基团的实例包括PAG基团、多糖、聚山梨醇酯以及这些基团的组合物。

[0158] 聚亚烷基二醇基团(PAG)由多个亚烷基二醇单体组成。在一个实施例中，所有单体是相同的(例如聚乙二醇(PEG)或聚丙二醇(PPG))。在另一个实施例中，亚烷基二醇单体是不同的。聚合体可以是无规共聚物(例如环氧乙烷和环氧丙烷的共聚物)，或者分枝或接枝共聚物。

[0159] 本文使用的“PEG”或聚乙二醇指任何水溶性聚乙二醇或聚氧化乙烯。聚乙二醇的化学结构式为-$(CH_2CH_2O)_n$-，其中n可以是从2到2000的整数。PEG的一端通常是相对没有活性的官能团，如烷基或烷氧基等。使用甲氧基封端的PEG命名为mPEG，结构式$CH_3O(CH_2CH_2O)_n$-，但一般仍然称为PEG。PEG20K指分子量为20,000聚乙二醇分子。

[0160] PEG另一端通常是活化官能团或者易于形成共价键的官能团，例如氨基、羧基、羟基、巯基、醛等。PEG-马来酰亚胺可以与半胱氨酸侧链的巯基通过迈克尔加成反应接合；PEG-碘代乙酰基(CO-CH_2-I)与巯基-SH反应形成稳定的硫醚键；PEG-NHS(琥珀酰亚胺)可以与氨基酸α氨基或赖氨酸侧链ε-氨基通过亲核取代反应(酰化)接合；PEG-醛与多肽上的氨基在还原剂(如氰基硼氢化钠)作用下可以通过还原性烷基化反应接合。

[0161] 本发明中使用的商业PEG试剂包括，但不局限于，mPEG-SC(甲氧基-PEG-琥珀酰亚胺基碳酸酯)、mPEG-NHS(SCM)(或mPEG-SPA，单甲氧基聚乙二醇丙酸琥珀酰亚胺酯)、NHS-PEG-NHS、mPEG-CHO(甲氧基-PEG-丙醛)、ALD-PEG-ALD(乙醛-PEG-乙醛)、PEG-Ts(甲氧基-PEG-甲苯磺酸)、Ts-PEG-Ts(甲苯磺酸-PEG-甲苯磺酸)、mPEG-CDI(甲氧基-PEG-羰基咪唑)、CDI-PEG-CDI(羰基咪唑-PEG-羰基咪唑)、mPEG-NPC(甲氧基-PEG-硝基苯基碳酸酯)、mPEG-ISC(PEG-异氰酸酯)、ISC-PEG-ISC(异氰酸酯-PEG-异氰酸酯)、mPEG-EPO(甲氧基-PEG-环氧化物)、EPO-PEG-EPO(环氧化物-PEG-环氧化物)、mPEG-Mal(甲氧基-PEG-马来酰亚胺)、Mal-PEG-Mal(马来酰亚胺-PEG-马来酰亚胺)、马来酰亚胺-PEG-NHS、马来酰亚胺-PEG-NH_2、马来酰亚胺-PEG-COOH、PEG-乙烯基砜衍生物、(VS-PEG-X、X＝NHS、马来酰亚胺、NH_2、COOH等)、PEG-碘代乙酰胺(iodo acetyl)衍生物(IA-PEG-X、X＝NHS、马来酰亚胺、NH_2、COOH等)、mPEG-OPSS(甲氧基-PEG-邻二硫吡啶(orthopyridyl disulfide))、OPSS-PEG-NHS(邻二硫吡啶-PEG-琥珀酰亚胺酯)、OPSS-PEG-NH_2、OPSS-PEG-OPSS。

[0162] 本发明中的PEG分子可以是直链的、支链的、分叉的或哑铃状的PEG。在一个实施例中，支链PEG可以用通式R(-PEG-$_n$OH)$_m$表示，其中R(通常是多羟基的)是核心基团，例如季戊

四醇、糖、赖氨酸或甘油;m代表支链数,可以是从2起到核心基团附着位点最大数目;n代表PEG片段的数量,每个支链上的PEG片段的数量可以不等。在另一个实施例中,支链PEG可以用通式$(CH_3O\text{-}PEG\text{-}_n)_pR\text{-}Z$表示,p等于2或3,R是赖氨酸或甘油,Z代表可以进行反应的活化官能团。在一个实施例中,分叉PEG用通式$PEG(\text{-}L\text{-}X)_n$表示,L是连接基,X是末端活化官能团。

[0163] PEG可以是多分散的,多分散指数小于1.05。PEG基团也可以是单分散的。单分散指PEG具有单一的长度(分子量),而不是各种近似长度(分子量)的混合物。

[0164] 术语烷基包括饱和的直链或支链烃基。

[0165] 术语烷氧基包括自由基"烷基-O-"。代表性的例子是甲氧基、乙氧基、丙氧基(例如1-丙氧基和2-丙氧基)、丁氧基(例如1-丁氧基、2-丁氧基和2-甲基-2-丙氧基)、戊氧基、己氧基等。

[0166] 糖基团

[0167] 本发明中的多肽或蛋白可以包含糖基化位点。糖基团能够改善药物的药效和药物动力学特征,并在药物寻靶和药物转运中起作用。糖基团可以是O-连接或N-连接。O-连接一般是在丝氨酸或苏氨酸羟基的氧原子上,N-连接是在天冬酰胺侧链酰胺的氮原子上。GLP-1受体结合多肽一般不会被糖基化。但GLP-1-PSSGAPPPS-IgG Fc中,C末端延伸的最后一个氨基酸残基丝氨酸可以被糖基化,而Fc的N末端第11个氨基酸苏氨酸残基(AEPKSCDKTHTCP…)也可以被糖基化。

[0168] 代表性糖基团包括但不局限于:甘油、单糖、二糖、三糖、寡糖和多糖如淀粉、糖原、纤维素和/或多糖树胶。特别的单糖包括C6及以上(特别是C6和C8)糖如葡萄糖、果糖、甘露糖、半乳糖、核酸糖或景天庚糖;二糖和三糖包括含有二或三个单糖单元(特别是C5至C8)的基团、例如蔗糖、纤维二糖、麦芽糖、乳糖和/或蜜三糖。

[0169] 其它亲水基团

[0170] 生物适合的聚阳离子基团包括骨架或侧链上具有多个氨基的聚胺基团,例如聚赖氨酸和其它天然或合成的氨基酸构成的具有多个正电荷的氨基酸聚合物,包括聚鸟氨酸,聚精氨酸,聚组氨酸,非多肽聚胺如聚氨基苯乙烯,聚氨基丙烯酸酯,聚-N甲基氨基丙烯酸酯,季胺聚合物等。生物适合的聚阴离子基团包括骨架或侧链上具有多个羧基的基团,如聚天冬氨酸,聚谷氨酸等。其它亲水基团包括天然或合成多糖,如壳聚糖、葡聚糖等。

[0171] 聚阴离子生物粘附剂

[0172] 某些亲水基团有潜在的生物粘附特性。这样的例子可见于美国专利US 6,197,346。这些具有多个羧基的聚合物显示生物粘附特性。降解时显露出多个羧基的快速生物降解聚合物,如乳酸羟基乙酸共聚物(poly(lactide-co-glycolide))、聚酐、聚原酸酯也都是生物粘附剂。这些聚合物可以把多肽或蛋白药物投放到胃肠道。聚合物降解时暴露出来的羧基可以牢固附着在胃肠道,协助投放多肽或蛋白药物。

[0173] 亲脂性基团

[0174] 在一个实施例中,修饰基团包括一个或多个亲脂性基团。亲脂性基团可以是本领域人员众所周知的,包括但不限于:烷基、链烯基、炔基、芳基、芳基烷基、烷基芳香基、脂肪酸、胆甾醇以及亲脂性多聚物和低聚物。

[0175] 烃基可以是饱和、非饱和、直链的、支链的或环烃,具有一个或多个碳原子。在一个实施例中,烃基有1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、

24、25、26、27、28、29、30或更多的碳原子。烃基可以是无取代，或有一个或者多个取代基。

[0176] 亲脂性基团也可以是脂肪酸，如天然的、合成的、饱和的、不饱和的、直链的或支链的脂肪酸。在一个实施例中，脂肪酸有2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24或更多个碳原子。

[0177] 结合策略

[0178] 蛋白与修饰基团的结合程度、结合点的选择、修饰基团的选择要根据需要而变化，例如使缀合物在体内不易降解，从而延长血浆半衰期。结合部位可能包括一个氨基酸残基，比如赖氨酸残基。在一个实施例中，蛋白缀合物是单结合物。在另一个实施例中，蛋白缀合物是多结合物。在另一个实施例中，蛋白缀合物是单结合物、双结合物、三结合物、四结合物等的混合物。修饰基团可以相同，也可以不同。当蛋白缀合物具有多个修饰基团时，一个或多个修饰基团最好通过可水解键与融合蛋白相连而其它一个或多个修饰基团最好通过不可水解键与融合蛋白相连。或者所有修饰基团都通过可水解键与融合蛋白相连，但各个修饰基团在体内的水解速率有快有慢。

[0179] 理想的结合策略是使缀合物具有原蛋白部分或全部生物活性。优选的胰岛素受体结合多肽的结合部位包括双链胰岛素类似物的B1-N末端、B链C末端原有或取代、插入后引入的赖氨酸侧链氨基或半胱氨酸侧链巯基、A链C末端取代或插入后引入的赖氨酸侧链氨基或半胱氨酸侧链巯基、单链胰岛素类似物的N末端或C末端原有或取代、插入后引入的赖氨酸侧链氨基或半胱氨酸侧链巯基。B1单结合物和B链双结合物是最常用的。另外可以通过在单链胰岛素类似物的C肽连接片段或A链、B链嵌入具有氨基或巯基的天然或非天然氨基酸来创造其它结合位点。白介素-1受体结合多肽最常用的结合位点包括84和116位的半胱氨酸侧链巯基或N末端的氨基。GLP-1类似物的最常用的结合位点包括GLP-1(7-37)-OH或GLP-1(7-36)-NH_2从N末端起第10位、20位和28位原有或取代、插入后引入的赖氨酸侧链氨基或半胱氨酸侧链巯基，或C末端取代或插入后引入的赖氨酸侧链氨基或半胱氨酸侧链巯基。Exendin-4类似物的最常用的结合位点包括Exendin-4从N末端起第12位、20位、27位、28位、32位原有、取代或插入后引入的赖氨酸侧链氨基或半胱氨酸侧链巯基，或C末端取代或插入的赖氨酸侧链氨基或半胱氨酸侧链巯基。

[0180] 修饰基团与蛋白可以通过可水解键(如酯，碳酸，可水解氨基甲酸酯)结合。可水解键使蛋白缀合物具有前药的效果。比如修饰基团的结合部位在蛋白对受体结合区，因此修饰基团与蛋白缀合物没有活性。当一个或多个修饰基团在一段时间内从蛋白缀合物脱离后，释放出活性蛋白。使用可水解键能够提供延时释放或缓释的效果。

[0181] 在一个实施例中，蛋白通过非水解键(如酰胺键，醚键)与修饰基团相连。必要时，非水解键有助于延长蛋白缀合物在血浆中的循环时间。

[0182] 蛋白或其类似物、衍生物可以通过各种亲核官能团与修饰基团相连，包括但不局限于亲核羟基或氨基。例如，丝氨酸、苏氨酸、酪氨酸具有亲核羟基，组氨酸、赖氨酸或胰岛素及其类似物的A链、B链N-末端都具有亲核氨基。胰岛素及其类似物也可以通过自由巯基-SH与修饰基团相连，例如形成硫酯、硫醚、磺胺键。

[0183] 分子量较小的多肽或蛋白化合物在血浆中的循环时间短的一个重要因素就是肾清除。增加多肽或蛋白化合物分子量直至超过40,000道尔顿(Da)这个肾清除临界点，可以显著降低肾清除率，延长多肽在体内作用时间。常用的方法是使多肽或蛋白与天然或合成

大分子形成可水解或不可水解键。生物大分子包括白蛋白、多糖(如葡聚糖)、抗体(如IgG)等。白蛋白和IgG占血浆蛋白的90％，有长达几周的体内循环时间。与白蛋白或IgG Fc结合的多肽的体内循环时间也可以显著延长。例如，etanercept就是可溶性TNF2受体结合IgG1 Fc的产物。这个150kDa的受体二聚物是一种有效的抗炎物质，每周给药两次($t_{1/2}$＝102小时)。近期批准的促进血小板生成的romiplostim是IgG融合蛋白的另外一个例子。

[0184] 白蛋白可以是人白蛋白(HSA)、人白蛋白类似物或人白蛋白的一部分。人白蛋白包含585个氨基酸残基，分子量66500。EP322,094提供了较短的人白蛋白序列，包括HAS(1-373)、HAS(1-388)、HAS(1-389)、HAS(1-369)、HAS(1-419)以及1-369和1-419之间的片段。EP399666提供的序列包括HAS(1-177)、HAS(1-200)以及HSA(1-177)和HAS(1-200)之间的片段。免疫球蛋白的Fc部分可以是人免疫球蛋白的Fc部分、人免疫球蛋白Fc部分的类似物、人免疫球蛋白Fc部分的片段等。Fc可以包括铰链区、C_H2、C_H3直到C末端。Fc融合蛋白延长体内循环时间的一个主要因素是Fc能够结合FcRn。FcRn分布在内皮细胞的表面，以pH依赖的方式与IgG结合，保护IgG不被降解。在CH_2和CH_3界面的变异可以延长IgG的半衰期(Hinton PR等,2004.Engineered human IgG antibodies with longer serum half-lives in primates.J Biol Chem.279(8):6213-6;Vaccaro C.等,2005.Engineering the Fc region of immunoglobulin G to modulate in vivo antibody levels.Nat Biotechnol.23(10):1283-8)。血管中70％的白蛋白是巯基白蛋白(mercaptalbumin)，其半胱氨酸-34的侧链巯基是血浆中活性最强的巯基。本发明的蛋白或其类似物、衍生物可以通过一个一端带有马来酰亚胺等活化官能团的连接基与其反应生成融合蛋白-白蛋白缀合物。在一种实施方式中，本发明的蛋白的N-末端或C-末端可以与白蛋白或免疫球蛋白Fc的N-末端或C-末端相连。这种结合策略使小分子量化合物的循环时间达到其结合的血浆蛋白的半衰期，但代价可能是降低的受体结合能力。解决方案之一就是在多肽(或蛋白)与修饰基团之间插入间隔基。间隔基例如β-丙氨酸、γ-氨基丁酸、γ-谷氨酸或聚乙二醇可以用于多肽/蛋白的一个氨基和一个修饰基团之间。Liraglutide的棕榈酸基团(plamitoyl group)通过一个间隔基与赖氨酸的侧链相连。另外的一个解决办法就是修饰基团通过一个“可逆”(“reversible”)连接基与多肽/蛋白相连。

[0185] 融合蛋白/二聚蛋白/交联蛋白

[0186] 本发明中涉及的融合蛋白、二聚蛋白或交联蛋白是GLP-1受体结合多肽、GIP受体结合多肽或胰岛素受体结合多肽与白介素-1受体拮抗蛋白的连接后的产物。两部分多肽/蛋白可以直接相连，也可以通过连接基(或间隔基)相连。融合蛋白/二聚蛋白/交联蛋白可以对白介素-1受体有IL-1RA的1％、5％、10％、20％、30％、40％、50％、60％、70％、80％、90％、100％或更高的生物活性，同时，根据另一部分是GLP-1受体结合多肽、GIP受体结合多肽或胰岛素受体结合多肽，对GLP-1受体、GIP受体或胰岛素受体分别有GLP-1(7-36)-NH_2、GIP(1-42)或人胰岛素的0.1％、0.2％、0.3％、0.4％、0.5％、1％、5％、10％、20％、30％、40％、50％、60％、70％、80％、90％、100％或更高的生物活性。

[0187] 本发明中的融合蛋白、二聚蛋白、交联蛋白及其衍生物可以使用生物工程技术制备和生产。为了蛋白表达和生产的便利，甲硫氨酸可以根据需要添加到本发明中各蛋白序列的N末端。

[0188] 连接基(或间隔基)可以是化学合成的分子，如长链脂肪酸或聚乙二醇，也可以是

天然或非天然氨基酸(如赖氨酸、谷氨酸、天冬氨酸)、短肽(如β-丙氨酸-β-丙氨酸)、蛋白，或一个或多个可选的长链脂肪酸、聚乙二醇、氨基酸、短肽等通过共价键连接而成的长链，或任何将两个活性多肽/蛋白通过共价键连接的结构，或缺失。

[0189] 连接基可以通过化学反应连接两个原不相连接的多肽/蛋白(一个是白介素-1受体拮抗蛋白，另外一个是GLP-1受体结合多肽、GIP受体结合多肽或胰岛素受体结合多肽)。在一种实施方式中，连接基可以有2个反应基团(例如N-羟基琥珀酰亚胺(NHS酯)或马来酰亚胺)，分别与白介素-1受体拮抗蛋白和GLP-1受体结合多肽(或GIP受体结合多肽或胰岛素受体结合多肽)上的氨基或巯基反应，使三个片段连为一体。在一种实施方式中，连接基可以有一个反应基团(例如NHS酯、马来酰亚胺、碘代乙酰基或乙烯砜)和一个功能基团(例如氨基或巯基)，分别与白介素-1受体拮抗蛋白和GLP-1受体结合多肽(或GIP受体结合多肽或胰岛素受体结合多肽)上的另外一个功能基团(氨基或巯基)和另外一个反应基团(例如NHS酯、马来酰亚胺、碘代乙酰基或乙烯砜)反应，使三个片段连为一体。在另一种实施方式中，连接基可以有两个功能基团(例如氨基或巯基)，分别与白介素-1受体拮抗蛋白和GLP-1受体结合多肽(或GIP受体结合多肽或胰岛素受体结合多肽)上的反应基团(例如NHS、马来酰亚胺、碘代乙酰基或乙烯砜)反应，使三个片段连为一体。反应基团和功能基团位于哪个片段，需要根据具体反应的要求而定。

[0190] 如果连接基已经与一个具有生物活性的多肽(例如白介素-1受体拮抗蛋白)相连，而要通过化学反应连接另外一个原不相连接的具有生物活性的多肽，反应方式与上述类似。与一个多肽相连的连接基和另一个不相连的多肽一个需要有功能基团(例如氨基或巯基)，另外一个需要有反应基团(例如NHS酯、马来酰亚胺、碘代乙酰基或乙烯砜)。至于反应基团和功能基团位于连接基或是多肽，需要根据具体反应的要求而定。

[0191] 在一个具体的实施方式中，连接基(或间隔基)含有一个或一个以上的赖氨酸或半胱氨酸，其侧链的氨基或巯基可用于与修饰基团反应。在一种实施方式中，GLP-1受体结合多肽、GIP受体结合多肽或胰岛素受体结合多肽与白介素-1受体拮抗蛋白通过短肽相连，成为一条单链融合蛋白。短肽的通式是$(GlyGlyGlyGlySer)_n$，n是0、1、2、3、4、5或6。

[0192] 1、GLP-1受体结合多肽和白介素-1受体拮抗蛋白的融合蛋白

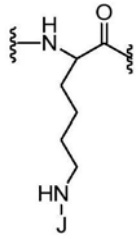
[0193] 在一个实施方式中，以人GLP-1为基础的GLP-1受体结合多肽序列是：

[0194] $X_{G1}X_{G2}X_{G3}GX_{G5}X_{G6}TSDX_{G10}SX_{G12}YLEX_{G16}X_{G17}X_{G18}AX_{G20}X_{G21}FIX_{G24}X_{G25}LX_{G27}X_{G28}X_{G29}X_{G30}X_{G31}$，其中，

[0195] X_{G1}是组氨酸、D-组氨酸、去氨基组氨酸(desamino histidine)、β-羟基-组氨酸、高组氨酸(homohistidine)、α-氟甲基(fluoromethyl)-组氨酸、α-甲基-组氨酸、N-甲基-组氨酸、N^{α}-乙酰基-组氨酸、α-甲基-组氨酸、2-吡啶-丙氨酸、3-吡啶-丙氨酸、4-吡啶-丙氨酸、咪唑丙酰(imidazopropionyl)；X_{G2}是2-甲基丙氨酸(Aib)、甘氨酸、D-丝氨酸、丝氨酸、苏氨酸、亮氨酸、异亮氨酸、丙氨酸、缬氨酸、氨基环丙烷羧酸、氨基环丁烷羧酸、氨基环戊烷羧酸、氨基环己烷羧酸、氨基环庚烷羧酸或氨基环辛烷羧酸；X_{G3}是谷氨酸、天冬氨酸或谷氨酰胺；X_{G5}是苏氨酸、天冬氨酸、谷氨酸、精氨酸、丙氨酸、赖氨酸或组氨酸；X_{G6}是苯丙氨酸、酪氨酸、色氨酸或组氨酸；X_{G10}是缬氨酸、酪氨酸、苯丙氨酸、色氨酸、组氨酸、亮氨酸、异亮氨酸、丝氨酸、苏氨酸、天冬氨酸、谷氨酸、丙氨酸、赖氨酸、精氨酸、半胱氨酸、通式1或通式2；X_{G12}是丝氨酸、异亮氨酸、赖氨酸、精氨酸、半胱氨酸、通式1或通式2；X_{G16}是甘氨酸、丝氨酸、组氨

酸、谷氨酸、天冬氨酸、谷氨酰胺、天冬酰胺、赖氨酸、精氨酸、高谷氨酸(homoglutamic acid)、半胱氨酸、高半胱氨酸(homocysteicacid)或磺丙氨酸(cysteic acid);X_{G17}是谷氨酰胺、精氨酸、异亮氨酸、谷氨酸、天冬氨酸、组氨酸、赖氨酸、半胱氨酸、通式1或通式2;X_{G18}是丙氨酸、精氨酸、组氨酸、谷氨酸或赖氨酸;X_{G20}是赖氨酸、精氨酸、天冬氨酸、谷氨酸、谷氨酰胺、组氨酸、2-甲基丙氨酸、半胱氨酸、通式1或通式2;X_{G21}是天冬氨酸、谷氨酸、亮氨酸、丙氨酸、赖氨酸、半胱氨酸、通式1或通式2;X_{G24}是丙氨酸、谷氨酰胺、天冬酰胺、谷氨酸、天冬氨酸、丝氨酸或组氨酸;X_{G25}是丙氨酸、色氨酸、苯丙氨酸、酪氨酸、半胱氨酸、赖氨酸、通式1或通式2;X_{G27}是缬氨酸、亮氨酸、赖氨酸、精氨酸、丙氨酸、甘氨酸、半胱氨酸、通式1或通式2;X_{G28}是赖氨酸、精氨酸、天冬氨酸、谷氨酸、丙氨酸、天冬酰胺、半胱氨酸、通式1或通式2;X_{G29}是甘氨酸、谷氨酰胺、苏氨酸、丝氨酸、赖氨酸、精氨酸、半胱氨酸、通式1或通式2;X_{G30}是精氨酸、赖氨酸、甘氨酸、组氨酸、半胱氨酸、通式1或通式2;X_{G31}是-NH_2、甘氨酸、苏氨酸、丝氨酸、天冬氨酸、谷氨酸、色氨酸、酪氨酸、苯丙氨酸、组氨酸、精氨酸、赖氨酸、半胱氨酸、连接基或间隔基、通式3、通式4或者连接基或间隔基+X_{G32},其中X_{G32}是赖氨酸、半胱氨酸、通式3、通式4或不存在;在一个具体实施方式中,X_{G31}是GPSSGAPPPS或PSSGAPPPS,其中任何一个氨基酸残基都可以被取代、删除或是通式1或通式2或通式3或通式4;

[0196] 本发明中,通式1的结构是:

[0197] 

[0198] 其中,J是L_n-M_L结构、-W-X-Y-Z结构或氢原子;

[0199] M_L是修饰基团,包括但不局限于-W-X-Y-Z、脂肪酸、聚乙二醇、白蛋白、IgG Fc、糖基团等;

[0200] L_n是可选的连接基、共价键或不存在;可选的连接基包括但不局限于:聚乙二醇、长链脂肪酸、多肽、天然或非天然氨基酸、或由一个或多个聚乙二醇分子、脂肪酸、多肽、氨基酸分子通过共价键连接形成的长链;在一种实施方式中,L_n可以是-NH-$(CH_2CH_2O)_n$-CH_2-CO-、-NH-$(CH_2)_n$-CO-、-NH-$(CH_2CH_2O)_n$-$(CH_2)_r$-CO-,n是1-25的整数,r是1-16的整数;在一种具体实施方式中,L_n是-NH-$(CH_2CH_2O)_2$-CH_2-CONH-$(CH_2CH_2O)_2$-CH_2-CO-;在一种实施方式中,L_n是-NH-$(CH_2)_{n1}$-O-$(CH_2CH_2O)_{n2}$-$(CH_2)_{n3}$-CO-,n1、n2、n3分别是1-18的整数;在一种实施方式中,L_n是-NH-$(CH_2)_{n1}$-$(OCH_2CH_2)_{n2}$-CO-,n1、n2分别是1-18的整数;在以上实施方式中,L_n通过来自加下划线的羰基碳的键与多肽的侧链氨基形成酰胺键,另一端与M_L形成共价键;在一种实施方式中,L_n通过来自加下划线的羰基碳的键与多肽的侧链氨基形成酰胺键,另一端与-W-X-Y-Z形成酰胺键;

[0201] 在本发明中,-W-X-Y-Z结构是:

[0202] W是侧链具有羧基的α-氨基酸残基,该残基以其羧基基团之一与多肽/蛋白N-末端氨基酸残基的α-氨基或与多肽/蛋白中的赖氨酸残基的ε-氨基或L_n末端的氨基一起形成酰胺基;

[0203] 或者W是由2、3或4个α-氨基酸通过酰胺键连接起来的链,所述通过酰胺键连接的

链连接至多肽/蛋白N-末端氨基酸残基的α-氨基或多肽/蛋白中赖氨酸残基的ε-氨基或L_n末端的氨基;W的氨基酸残基选自具有中性侧链的氨基酸残基和/或侧链具有羧基的氨基酸残基,使得W含有至少一个在侧链具有羧基的氨基酸残基;

[0204] 或者W是从X到多肽/蛋白N-末端氨基酸的α-氨基或多肽/蛋白中的赖氨酸残基的ε-氨基或L_n末端的氨基的共价键;

[0205] X是-CO-、-CH(COOH)CO-、-N(CH_2COOH)CH_2CO-、-N(CH_2COOH)$CH_2CON(CH_2COOH)CH_2$CO-、-N(CH_2CH_2COOH)CH_2CH_2CO-、-NHCH(COOH)$(CH_2)_4NH$CO-、-N(CH_2CH_2COOH)$CH_2CH_2CON(CH_2CH_2COOH)CH_2CH_2$CO-、-N($CH_2CH_2COOH$)$CH_2$CO-或者-N($CH_2COOH$)$CH_2CH_2$CO-,其中,

[0206] a)当W是氨基酸残基或氨基酸残基链时,上述X通过由加下划线的羰基碳的键与W中的氨基形成酰胺键;或者

[0207] b)当W是共价键时,上述X通过来自加下划线的羰基碳的键与多肽/蛋白的N-末端氨基酸残基的α-氨基或多肽/蛋白中的赖氨酸残基的ε-氨基或L_n末端的氨基形成酰胺键;

[0208] Y是-$(CH_2)_m$,其中m是6-32的整数;

[0209] 或包含1、2或3个-CH=CH-基团和多个-CH_2-基团的二价烃链,所述多个-CH_2-基团的个数满足烃链中的碳原子总数范围是10-32;

[0210] 或通式-$(CH_2)_vC_6H_4(CH_2)_w$-的二价烃链,其中v和w是整数,或者它们之一是零,使得v和w总和的范围是6-30;且

[0211] Z是-COOH、-CO-Asp、-CO-Glu、-CO-Gly、-CO-Sar、-$CH(COOH)_2$、-$N(CH_2COOH)_2$、-SO_3H、-PO_3H或不存在;条件是当W是共价键且X是-CO-时,Z不是-COOH;

[0212] 侧链-W-X-Y-Z的中W可以是共价键;另一方面,W可以是侧链具有羧基的α-氨基酸残基,包括一共4-10个碳原子;W可以是由遗传密码子编码的α-氨基酸残基,例如,W可以选自α-Asp、β-Asp、α-Glu和γ-Glu组成的组;W的其它选择例如是α-hGlu或者δ-hGlu;

[0213] 在另一个实施方式中,W是由两个α-氨基酸残基组成的链,其中一个α-氨基酸残基具有4-10个碳原子且侧链具有羧基,而另一个具有2-11个碳原子但没有自由羧基;所述的没有自由羧基的α-氨基酸残基可以是中性的可编码的α-氨基酸残基;根据这种实施方式的W的例子是:α-Asp-Gly、Gly-α-Asp、β-Asp-Gly、Gly-β-Asp、α-Glu-Gly、Gly-α-Glu、γ-Glu-Gly、Gly-γ-Glu、α-hGlu-Gly、Gly-α-hGlu、δ-hGlu-Gly和Gly-δ-hGlu;

[0214] 在另一个实施方式中,W是由两个α-氨基酸残基组成的链,两个α-氨基酸残基分别具有4-10个碳原子,侧链上均具有羧基;这些α-氨基酸残基之一或两个可以是可编码的α-氨基酸残基;根据这一实施方式的W的例子是:α-Asp-α-Asp、α-Asp-α-Glu、α-Asp-α-hGlu、α-Asp-β-Asp、α-Asp-γ-Glu、α-Asp-δ-hGlu、β-Asp-α-Asp、β-Asp-α-Glu、β-Asp-α-hGlu、β-Asp-β-Asp、β-Asp-γ-Glu、β-Asp-δ-hGlu、α-Glu-α-Asp、α-Glu-α-Glu、α-Glu-α-hGlu、α-Glu-β-Asp、α-Glu-γ-Glu、α-Glu-δ-hGlu、γ-Glu-α-Asp、γ-Glu-α-Glu、γ-Glu-α-hGlu、γ-Glu-β-Asp、γ-Glu-γ-Glu、γ-Glu-δ-hGlu、α-hGlu-α-Asp、α-hGlu-α-Glu、α-hGlu-α-hGlu、α-hGlu-β-Asp、α-hGlu-γ-Glu、α-hGlu-δ-hGlu、δ-hGlu-α-Asp、δ-hGlu-α-Glu、δ-hGlu-α-hGlu、δ-hGlu-β-Asp、δ-hGlu-γ-Glu和δ-hGlu-δ-hGlu;

[0215] 在另一个实施方式中,W是由三个分别具有4-10个碳原子的α-氨基酸残基组成的链,该链的氨基酸残基选自具有中性侧链的残基和/或侧链具有羧基的残基,使得该链含有至少一个侧链具有羧基的残基;在一个实施方式中,所述氨基酸残基是可编码的残基;

[0216] 在另一个实施方式中，W是由四个分别具有4-10个碳原子的α-氨基酸残基组成的链，该链的氨基酸残基选自具有中性侧链的残基和/或侧链具有羧基的残基，使得该链含有至少一个侧链具有羧基的残基；在一个实施方式中，所述氨基酸残基是可编码的残基；

[0217] 在一个实施方式中，-W-X-Y-Z中的W可以通过脲衍生物连接至赖氨酸残基的ε-氨基；

[0218] 侧链-W-X-Y-Z中的X可以是通式-C(=O)-的基团，通过来自加下划线的羰基碳的键与W中的氨基形成酰胺键；或当W是共价键时，X通过来自加下划线的羰基碳的键与多肽/蛋白的N-末端的α-氨基或多肽/蛋白中的赖氨酸残基的ε-氨基或L_n末端的氨基形成酰胺键；

[0219] 在进一步的实施方式中，所述侧链-W-X-Y-Z中的X可以是通式-CH(COOH)C(=O)-的基团，通过来自加下划线的羰基碳的键与W中的氨基形成酰胺键；或当W是共价键时，X通过来自加下划线的羰基碳的键与多肽/蛋白的N-末端的α-氨基或多肽/蛋白中的赖氨酸残基的ε-氨基或L_n末端的氨基形成酰胺键；

[0220] 在进一步的实施方式中，侧链-W-X-Y-Z中的X可以是通式-N(CH_2COOH)CH_2C(=O)-的基团，通过来自加下划线的羰基碳的键与W中的氨基形成酰胺键；或当W是共价键时，X通过来自加下划线的羰基碳的键与多肽/蛋白的N-末端的α-氨基或多肽/蛋白中的赖氨酸残基的ε-氨基或L_n末端的氨基形成酰胺键；

[0221] 在进一步的实施方式中，侧链-W-X-Y-Z中的X可以是通式-N(CH_2CH_2COOH)CH_2C(=O)-的基团，通过来自加下划线的羰基碳的键与W中的氨基形成酰胺键；或当W是共价键时，X通过来自加下划线的羰基碳的键与多肽/蛋白的N-末端的α-氨基或多肽/蛋白中的赖氨酸残基的ε-氨基或L_n末端的氨基形成酰胺键；

[0222] 在进一步的实施方式中，-W-X-Y-Z中的X可以是通式-N(CH_2COOH)CH_2CH_2C(=O)-的基团，通过来自加下划线的羰基碳的键与W中的氨基形成酰胺键；或当W是共价键时，X通过来自加下划线的羰基碳的键与多肽/蛋白的N-末端的α-氨基或多肽/蛋白中的赖氨酸残基的ε-氨基或L_n末端的氨基形成酰胺键；

[0223] 在进一步的实施方式中，-W-X-Y-Z中的X可以是通式-N(CH_2COOH)$CH_2CON(CH_2COOH)CH_2$C(=O)-的基团，通过来自加下划线的羰基碳的键与W中的氨基形成酰胺键；或当W是共价键时，X通过来自加下划线的羰基碳的键与多肽/蛋白的N-末端的α-氨基或多肽/蛋白中的赖氨酸残基的ε-氨基或L_n末端的氨基形成酰胺键；

[0224] 在进一步的实施方式中，-W-X-Y-Z中的X可以是通式-N(CH_2CH_2COOH)CH_2CH_2C(=O)-的基团，通过来自加下划线羰基碳的键与W中的氨基形成酰胺键；或当W是共价键时，X通过来自加下划线的羰基碳的键与多肽/蛋白的N-末端的α-氨基或多肽/蛋白中的赖氨酸残基的ε-氨基或L_n末端的氨基形成酰胺键；

[0225] 在进一步的实施方式中，-W-X-Y-Z中的X可以是通式-N(CH_2CH_2COOH)$CH_2CH_2CON(CH_2CH_2COOH)CH_2CH_2$C(=O)-的基团，通过来自加下划线的羰基碳的键与W中的氨基形成酰胺键；或当W是共价键时，X通过来自加下划线的羰基碳的键与多肽/蛋白的N-末端的α-氨基或多肽/蛋白中的赖氨酸残基的ε-氨基或L_n末端的氨基形成酰胺键；

[0226] 侧链-W-X-Y-Z中的Y可以是通式-$(CH_2)_m$基团，其中m是6-32、8-20、12-20或12-16的整数；

[0227] 在另一种实施方式中，-W-X-Y-Z中的Y是包含1、2或3个-CH=CH-基团和多个-CH_2-

基团的二价烃链，所述多个-CH_2-基团的个数满足烃链中的碳原子总数范围是6-32、10-32、12-20或12-16；

[0228] 在另一种实施方式中，-W-X-Y-Z中的Y是通式-$(CH_2)_vC_6H_4(CH_2)_w$-的二价烃链，其中v和w是整数，或者其中之一是零，使得v和w总和的范围是6-30、10-20或12-16；

[0229] 在一种实施方式中，侧链-W-X-Y-Z中的Z是-COOH，条件是当W是共价键而X是-CO-时，Z不是-COOH；

[0230] 在另一种实施方式中，-W-X-Y-Z中的Z是-CO-Asp、-CO-Glu、-CO-Gly、-CO-Sar、-$CH(COOH)_2$、-$N(CH_2COOH)_2$、-SO_3H或-PO_3H；

[0231] 在进一步的实施方式中，-W-X-Y-Z中的W是α-Asp、β-Asp、α-Glu或γ-Glu；X是-CO-或者-CH(COOH)CO-；Y是-$(CH_2)_m$，其中m是12-18的整数；Z是-COOH-、-$CH(COOH)_2$或不存在；

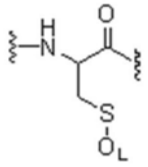
[0232] 在另一种实施方式中，-W-X-Y-Z中的W是α-Asp、β-Asp、α-Glu或γ-Glu；-X-Y-Z是-$\underline{C}O(CH_2)_nCH_3$，通过来自加下划线的羰基碳的键与W中的氨基形成酰胺键，其中n是10-20中的整数；

[0233] 在更具体的实施方式中，-W-X-Y-Z中的W是α-Asp、β-Asp、α-Glu或γ-Glu；-X-Y-Z是-$CO(CH_2)_{12}CH_3$；

[0234] 在更具体的实施方式中，-W-X-Y-Z中的W是α-Asp、β-Asp、α-Glu或γ-Glu；-X-Y-Z是-$CO(CH_2)_{14}CH_3$；

[0235] 在更具体的实施方式中，-W-X-Y-Z中的W是α-Asp、β-Asp、α-Glu或γ-Glu；-X-Y-Z是-$CO(CH_2)_{16}CH_3$；

[0236] 本发明中，通式2的结构是：

[0237] 

[0238] 其中，

[0239] O_L的基本结构是M_r-L_r-NH-J、M_r-L_r-Z_1、M_r-L_r-M_r或M_r-L_r-M_L或氢原子；

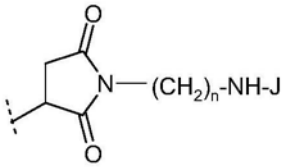
[0240] J和M_L如本发明上文中所定义；

[0241] M_r是能够与巯基反应形成共价键的功能团，例如马来酰亚胺、乙烯砜或碘代乙酰基等；L_r是可选的连接基、共价键或不存在，包括但不局限于：聚乙二醇、长链脂肪酸、或由一个或多个聚乙二醇分子和长链脂肪酸分子通过共价键连接形成的长链化合物；

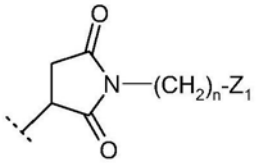
[0242] M_r-L_r-M_r中L_r两端的M_r可以相同，也可以不同；M_r-L_r-M_r通过一端的M_r与IL-1ra反应后形成共价键连接；

[0243] 当M_L是免疫球蛋白或IgG Fc时，连接基一端是M_r与IL-1ra连接，另外一端是醛，通过还原烷基化(reductive amination)与免疫球蛋白或IgG Fc上的氨基反应形成共价键；M_L包括人免疫球蛋白重链或轻链的所有或部分恒定区；免疫球蛋白部分可以包含除人免疫球蛋白(如IgG，IgA，IgM或IgE)重链恒定区的第一个结构域外的所有恒定区；每个免疫球蛋白部分的任何氨基酸残基都可以缺失或用一个或多个氨基酸残基取代，或可以插入一个或多个氨基酸残基；

[0244] O_L包括，但不限于以下结构：

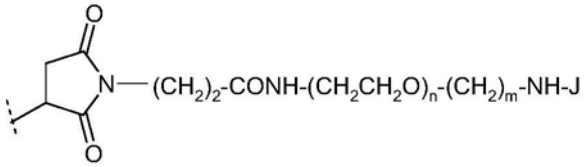

O
N
(CH2)n-NH-J
O

，

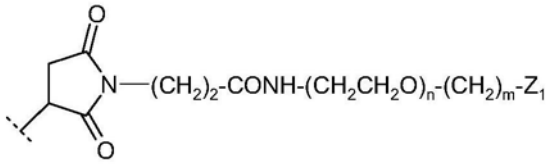

O
N
(CH2)n-Z1
O

，

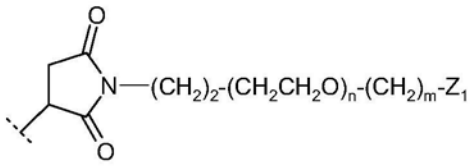
[0245]


O
N
(CH2)2-CONH-(CH2CH2O)n-(CH2)m-NH-J
O

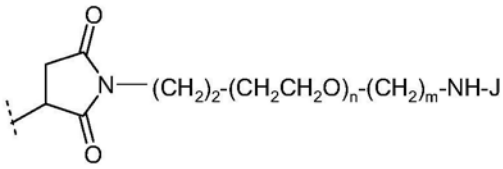
，

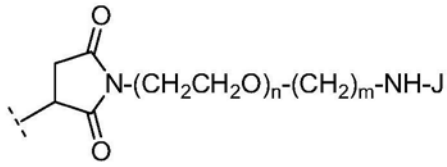

O
N
(CH2)2-CONH-(CH2CH2O)n-(CH2)m-Z1
O

，

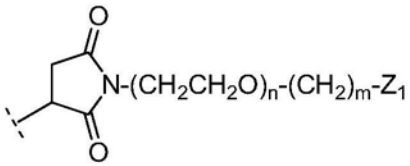


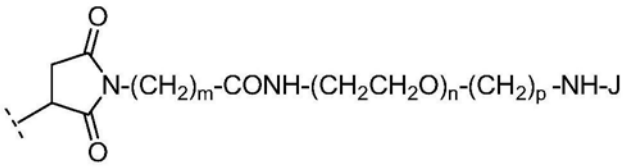
，

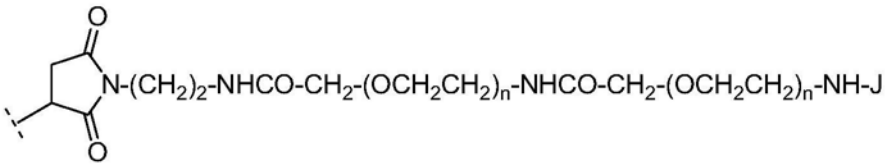


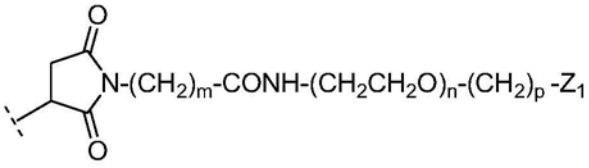


，

[0246] 







[0247] -$\underline{C}$H$_2$-CONH-(CH$_2$)$_n$-NH-J，通过来自下划线碳原子的键与半胱氨酸的硫原子形成硫醚键；

[0248] -$\underline{C}$H$_2$-CONH-(CH$_2$)$_n$-Z$_1$，通过来自下划线碳原子的键与半胱氨酸的硫原子形成硫醚键；

[0249] -$\underline{C}H_2$-CONH-$(CH_2CH_2O)_n$-$(CH_2)_m$-NH-J，通过来自下划线碳原子的键与半胱氨酸的硫原子形成硫醚键；

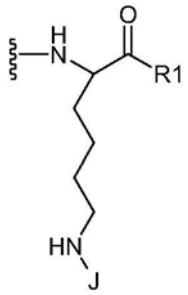
[0250] -$\underline{C}H_2$-CONH-$(CH_2CH_2O)_n$-$(CH_2)_m$-Z_1，通过来自下划线碳原子的键与半胱氨酸的硫原子形成硫醚键；

[0251] -$\underline{C}H_2$-CH_2-SO_2-$(CH_2CH_2O)_n$-$(CH_2)_m$-NH-J，通过来自下划线碳原子的键与半胱氨酸的硫原子形成硫醚键；

[0252] -$\underline{C}H_2$-CH_2-SO_2-$(CH_2CH_2O)_n$-$(CH_2)_m$-Z_1，通过来自下划线碳原子的键与半胱氨酸的硫原子形成硫醚键；

[0253] 其中Z_1是-COOH、-CO-Asp、-CO-Glu、-CO-Gly、-CO-Sar、-$CH(COOH)_2$、-$N(CH_2COOH)_2$、-SO_3H、-PO_3H或不存在；m、n、p分别是1-25的整数；

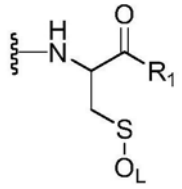
[0254] 本发明中，通式3的结构是：

[0255] 

，

[0256] J和O_L如上文所定义的；R_1是-OH或-NH_2；

[0257] 本发明中，通式4的结构是：

[0258] 

[0259] R_1和O_L如上文所定义。

[0260] 在一个实施方式中，GLP-1受体结合多肽的序列为：

[0261] $HX_{G2}EGTFTSDX_{G10}SSYLEX_{G16}QAAX_{G20}EFIAWLVX_{G28}GRX_{G31}$，其中，各变量如上文所定义的。

[0262] 在一个实施方式中，以exendin-4为基础的GLP-1受体结合多肽的序列为：

[0263] $X_{E1}X_{E2}X_{E3}GTX_{E6}TSDX_{E10}SX_{E12}X_{E13}X_{E14}EX_{E16}X_{E17}AX_{E19}X_{E20}X_{E21}FX_{E23}X_{E24}X_{E25}LX_{E27}X_{E28}X_{E29}X_{E30}X_{E31}X_{E32}X_{E33}X_{E34}X_{E35}X_{E36}X_{E37}X_{E38}X_{E39}$，其中，

[0264] X_{E1}是组氨酸、D-组氨酸、去氨基组氨酸、β-羟基-组氨酸、高组氨酸、α-氟甲基-组氨酸、α-甲基-组氨酸、N-甲基-组氨酸、N^{α}-乙酰基-组氨酸、α-甲基-组氨酸、2-吡啶-丙氨酸、3-吡啶-丙氨酸、4-吡啶-丙氨酸、咪唑丙酰(imidazopropionyl)、精氨酸或酪氨酸；X_{E2}是甘氨酸、丙氨酸、2-甲基丙氨酸、D-丝氨酸、丝氨酸、苏氨酸、亮氨酸、异亮氨酸、缬氨酸、氨基环丙烷羧酸、氨基环丁烷羧酸、氨基环戊烷羧酸、氨基环己烷羧酸、氨基环庚烷羧酸或氨基环辛烷羧酸；X_{E3}是天冬氨酸、谷氨酸或谷氨酰胺；X_{E6}是苯丙氨酸、丙氨酸、酪氨酸或萘基丙氨酸；X_{E10}是亮氨酸、异亮氨酸、酪氨酸、缬氨酸、丙氨酸、赖氨酸、半胱氨酸、通式1、通式2或五甘氨酸(pentylglycine)；X_{E12}是赖氨酸、半胱氨酸、精氨酸、丝氨酸、异亮氨酸或通式1或通式2；X_{E13}是谷氨酰胺、丙氨酸或酪氨酸；X_{E14}是甲硫氨酸、亮氨酸、正亮氨酸(norleucine)、异

亮氨酸、丙氨酸、缬氨酸或通式1或通式2；X_{E16}是谷氨酸、天冬氨酸、丝氨酸、甘氨酸、赖氨酸或精氨酸；X_{E17}是谷氨酸、谷氨酰胺、精氨酸或异亮氨酸；X_{E19}是缬氨酸、丙氨酸或谷氨酰胺；X_{E20}是赖氨酸、谷氨酰胺、半胱氨酸、精氨酸或通式1或通式2；X_{E21}是亮氨酸、谷氨酸或天冬氨酸；X_{E23}是异亮氨酸、亮氨酸、缬氨酸、五甘氨酸；X_{E24}是丙氨酸、谷氨酸、天冬氨酸、天冬酰胺或谷氨酰胺；X_{E25}是丙氨酸、色氨酸、苯丙氨酸、酪氨酸、半胱氨酸、赖氨酸、萘基丙氨酸、通式1或通式2；X_{E27}是赖氨酸、半胱氨酸、天冬酰胺、亮氨酸、缬氨酸、精氨酸、通式1或通式2；X_{E28}是天冬酰胺、赖氨酸、半胱氨酸、精氨酸、丙氨酸、通式1或通式2；X_{E29}是-NH_2、甘氨酸、谷氨酰胺、苏氨酸、赖氨酸、半胱氨酸或缺失；X_{E30}是-NH_2、甘氨酸、酪氨酸、精氨酸、赖氨酸、半胱氨酸、通式1、通式2或缺失；X_{E31}是-NH_2、甘氨酸、脯氨酸、高脯氨酸、硫代脯氨酸、N-烷基丙氨酸或缺失；X_{E32}是丝氨酸、赖氨酸、半胱氨酸、缺失、通式1或通式2；X_{E33}是丝氨酸、赖氨酸、半胱氨酸、通式1、通式2或缺失；X_{E34}是甘氨酸、缺失、通式1或通式2；X_{E35}是丙氨酸、赖氨酸、半胱氨酸、通式1、通式2或缺失；X_{E36}是脯氨酸、高脯氨酸、硫代脯氨酸、N-烷基丙氨酸或缺失；X_{E37}是脯氨酸、高脯氨酸、硫代脯氨酸、N-烷基丙氨酸或缺失；X_{E38}是脯氨酸、高脯氨酸、硫代脯氨酸、N-烷基丙氨酸或缺失；X_{E39}是丝氨酸、丝氨酸-NH_2、半胱氨酸、半胱氨酸-NH_2、赖氨酸、赖氨酸-NH_2或缺失，或是连接基或间隔基+X_{E40}，X_{E40}是赖氨酸、半胱氨酸、通式3或通式4。

[0265] 在一个实施方式中，以exendin-4为基础的GLP-1受体结合多肽的序列为

[0266] X_{E1}GEGTFTSDLSX_{E12}QX_{E14}EEEAVX_{E20}LFIEWL$X_{E27}X_{E28}X_{E29}X_{E30}X_{E31}X_{E32}X_{E33}X_{E34}X_{E35}X_{E36}X_{E37}X_{E38}X_{E39}$，其中，各变量如上文中所定义的。

[0267] 在一种实施方式中，exendin-4类似物的氨基酸序列与野生型序列相比有一个或多个氨基酸残基被半胱氨酸或赖氨酸取代，例如半胱氨酸或赖氨酸取代位于C末端，第20位的精氨酸、25位色氨酸、30位的甘氨酸、35位丙氨酸、39位丝氨酸或其它位点。

[0268] 从以上的论述可以看出，GLP-1受体结合多肽和白介素-1受体拮抗蛋白能够通过相似或不同的机理保护胰岛β细胞，治疗糖尿病。因此，将两种多肽连接后形成的融合蛋白、二聚蛋白、交联蛋白可以通过两种多肽的协同作用，达到比单独使用其中一种多肽更优异的治疗效果。另外，GLP-1受体的一个主要分布组织就是胰岛。GLP-1受体结合多肽可以为融合蛋白起到靶向作用，使白介素-1受体拮抗蛋白富集于胰岛及胰岛周围，更有效地发挥消炎等作用。

[0269] GLP-1受体结合多肽与白介素-1受体拮抗蛋白通过可选的连接基(或间隔基)相连，可以有多种不同的连接方式。

[0270] (1)GLP-1受体结合多肽-连接基或间隔基-白介素-1受体拮抗蛋白融合蛋白。

[0271] 在一个实施方式中，GLP-1受体结合多肽与白介素-1受体拮抗蛋白通过连接基形成单链化合物，所述融合蛋白的结构为(从左到右对应氨基酸序列从N末端到C末端)：

[0272] GLP-1受体结合多肽-连接基或间隔基-白介素-1受体拮抗蛋白；或者

[0273] 白介素-1受体拮抗蛋白-连接基或间隔基-GLP-1受体结合多肽。

[0274] 在一个实施方式中，以exendin-4和白介素-1受体拮抗蛋白为基础的融合蛋白的序列是：

[0275] $X_{E1}X_{E2}X_{E3}$GTX_{E6}TSDX_{E10}S$X_{E12}X_{E13}X_{E14}$E$X_{E16}X_{E17}$A$X_{E19}X_{E20}X_{E21}$F$X_{E23}X_{E24}X_{E25}$L$X_{E27}X_{E28}X_{E29}X_{E30}X_{E31}X_{E32}X_{E33}X_{E34}X_{E35}X_{E36}X_{E37}X_{E38}X_{E39}$-$L_j$-$X_{IL0}$RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX_{IL66}LSX_{IL69}VKSGDETRLQLEAVX_{IL84}ITDLSENRKQDKRFAFIRSDSGPTTS

FESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE,其中,各变量的含义如上文所定义的。

[0276] 在一个实施方式中,以exendin-4和白介素-1受体拮抗蛋白为基础的融合蛋白序列为:

[0277] X$_{E1}$X$_{E2}$EGTFTSDX$_{E10}$SX$_{E12}$QX$_{E14}$EEEAVX$_{E20}$LFIEWLX$_{E27}$X$_{E28}$X$_{E29}$X$_{E30}$X$_{E31}$X$_{E32}$X$_{E33}$X$_{E34}$X$_{E35}$X$_{E36}$X$_{E37}$X$_{E38}$X$_{E39}$-L$_j$-X$_{IL0}$RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE,各变量的含义如上文所定义的。

[0278] 在一个实施方式中,以exendin-4和白介素-1受体拮抗蛋白为基础的融合蛋白序列为:

[0279] HX$_{E2}$EGTFTSDX$_{E10}$SX$_{E12}$QX$_{E14}$EEEAVX$_{E20}$LFIEWLX$_{E27}$X$_{E28}$X$_{E29}$X$_{E30}$(PX$_{E32}$X$_{E33}$GX$_{E35}$PPPX$_{E39}$)$_{t2}$-L$_j$-X$_{IL0}$RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE,其中t2是0或1,其它变量如上文所定义的。

[0280] 在一个实施方式中,以exendin-4和白介素-1受体拮抗蛋白为基础的融合蛋白序列为:

[0281] HX$_{E2}$EGTFTSDX$_{E10}$SX$_{E12}$QX$_{E14}$EEEAVX$_{E20}$LFIEWLX$_{E27}$X$_{E28}$X$_{E29}$X$_{E30}$(PX$_{E32}$X$_{E33}$GX$_{E35}$PPPX$_{E39}$)$_{t2}$-(GGGGS)$_m$-X$_L$-(GGGGS)$_n$-X$_{IL0}$RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE,其中,

[0282] m、n分别是0、1、2、3、4、5或6;X$_L$是半胱氨酸、赖氨酸、缺失、通式1或通式2;t2是0或1;其它变量如上文所定义的。

[0283] 在一个实施方式中,融合蛋白的序列为:

[0284] HGEGTFTSDLSX$_{E12}$QMEEEAVRLFIEWLX$_{E27}$NGGPSSGAPPPS-(GGGGS)$_m$-X$_L$-(GGGGS)$_n$-X$_{IL0}$RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE,其中

[0285] m、n分别是0、1、2、3、4、5或6;其它变量如上文所定义的。

[0286] 在一个实施方式中,融合蛋白的序列为:

[0287] HGEGTFTSDLSX$_{E12}$QMEEEAVRLFIEWLX$_{E27}$NGGPSSGAPPPX$_{E39}$-(GGGGS)$_n$-X$_{IL0}$RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE,其中n是0、1、2、3、4、5或6,其它变量如上文中所定义的。

[0288] 在一个实施方式中,融合蛋白的序列为:

[0289] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-(GGGGS)$_n$-X$_{IL0}$RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-O$_L$)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子),其中,

[0290] n是0、1、2、3、4、5或6;其它变量如上文中所定义的。

[0291] 在一个实施方式中,融合蛋白的序列为:

[0292] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-(GGGGS)$_n$-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-O_L)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAME ADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子),其中,

[0293] n是0、1、2、3、4、5或6;其它变量如上文中所定义的。

[0294] 在一个实施方式中,以GLP-1和白介素受体拮抗蛋白为基础的融合蛋白的序列是:

[0295] $X_{G1}X_{G2}X_{G3}GX_{G5}X_{G6}TSDX_{G10}SX_{G12}YLEX_{G16}X_{G17}X_{G18}AX_{G20}X_{G21}FIX_{G24}X_{G25}LX_{G27}X_{G28}X_{G29}X_{G30}X_{G31}$-$L_j$-$X_{IL0}$RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX_{IL66}LSX_{IL69}VKSGDETRLQLEAVX_{IL84}ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX_{IL116}PGWFLX_{IL122}TAMEADQPVSLTNMPDEGVMVTKFYFQEDE;其中,各变量如上文中所定义的。

[0296] 在一个实施方式中,融合蛋白的序列为:

[0297] HX_{G2}EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLVX_{G28}GRX_{G31}-L_j-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVX_{IL84}ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX_{IL116}PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE,其中,各变量如上文中所定义的。

[0298] 在一个实施方式中,融合蛋白的序列为:

[0299] HX_{G2}EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLVX_{G28}GRX_{G31}-(GGGGS)$_m$-X_L-(GGGGS)$_n$-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVX_{IL84}ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX_{IL116}PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;其中,m、n分别是0、1、2、3、4、5或6;其它变量如上文中所定义的。

[0300] 在一个实施方式中,融合蛋白的序列为:

[0301] HX_{G2}EGTFTSDX_{G10}SSYLEX_{G16}QAAX_{G20}EFIAWLVX_{G28}GRG-(GGGGS)$_m$-X_L-(GGGGS)$_n$-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX_{IL116}PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE,其中,m、n分别是0、1、2、3、4、5或6;其它变量如上文中所定义的。

[0302] 在一个实施方式中,融合蛋白的序列为:

[0303] HX_{G2}EGTFTSDX_{G10}SSYLEX_{G16}QAAX_{G20}EFIAWLVX_{G28}GRX_{G31}-(GGGGS)$_n$-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX_{IL116}PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE,其中,n是0、1、2、3、4、5或6;其它变量如上文中所定义的。

[0304] 在一个实施方式中,融合蛋白的序列为:

[0305] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGRG-(GGGGS)$_n$-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-O_L)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子),其中,n是0、1、2、3、4、5或6;其它变量如上文中所定义的。

[0306] 在一个实施方式中,融合蛋白的序列为:

[0307] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGRG-(GGGGS)$_n$-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-O_L)ITDLSEN

RKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子),其中,n是0、1、2、3、4、5或6;其它变量如上文中所定义的。

[0308] 在一个实施方式中,融合蛋白的序列为:

[0309] $HX_{G2}EGTFTSDX_{G10}SSYLEX_{G16}QAAX_{G20}EFIAWLVX_{G28}GRPSSGAPPPS-(GGGGS)_m-X_L-(GGGGS)_n-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX_{IL116}CPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE$,其中,m、n分别是0、1、2、3、4、5或6;$X_L$是半胱氨酸、赖氨酸或缺失,或是通式1或通式2;其它变量如上文中所定义的。

[0310] 在一个实施方式中,融合蛋白的序列为:

[0311] $HX_{G2}EGTFTSDX_{G10}SSYLEX_{G16}QAAX_{G20}EFIAWLVX_{G28}GRPSSGAPPPX_{G39}-(GGGGS)_n-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX_{IL116}PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE$,其中n分别是0、1、2、3、4、5或6;其它变量如上文中所定义的。

[0312] 在一个实施方式中,融合蛋白的序列为:

[0313] $HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGRPSSGAPPPS-(GGGGS)_n-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-O_L)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE$(S是半胱氨酸侧链的硫原子),其中,n是0、1、2、3、4、5或6;其它变量如上文中所定义的。

[0314] 在一个实施方式中,融合蛋白的序列为:

[0315] $HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGRPSSGAPPPS-(GGGGS)_n-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-O_L)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE$(S是半胱氨酸侧链的硫原子),其中,n是0、1、2、3、4、5或6;其它变量如上文中所定义的。

[0316] 在一个实施方式中,GLP-1受体结合多肽与白介素-1受体拮抗蛋白与生物大分子形成单链化合物,所述融合蛋白的结构为(从左到右对应氨基酸序列从N末端到C末端):

[0317] GLP-1受体结合多肽-连接基(或间隔基)-生物大分子-连接基(或间隔基)-白介素-1受体拮抗蛋白;

[0318] GLP-1受体结合多肽-连接基(或间隔基)-白介素-1受体拮抗蛋白-连接基(或间隔基)-生物大分子;其中生物大分子可以是白蛋白或IgG Fc等。

[0319] 在一个实施方式中,包含人白蛋白融合蛋白的序列为:

[0320] $HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-(GGGGS)_m-$DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL-(GGGGS)$_n$-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQ

LVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDS GPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE,其中,m、n分别是0、1、2、3、4、5或6;其它变量如上文中所定义的。

[0321] 在一个实施方式中,人白蛋白融合蛋白的序列为:

[0322] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-(GGGGS)$_m$-X_{IL0}RPSGRKSSKMQAFRIW DVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENR KQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_n$-DAHKSE VAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRE TYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFA KRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFV ESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQN LIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCV LHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPK ATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL,其中,m、n分别是0、1、2、3、4、5或6;其它变量如上文中所定义的。

[0323] 在一个实施方式中,人白蛋白融合蛋白的序列为:

[0324] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGRG-(GGGGS)$_m$-DAHKSEVAHRFKDLGEENFKALVL IAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNE CFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAA CLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLE CADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLG MFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQ NALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVE KCCKADDKETCFAEEGKKLVAASQAALGL-(GGGGS)$_n$-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGY LQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTS FESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE,其中,m、n分别是0、1、2、3、4、5或6;其它变量如上文中所定义的。

[0325] 在一个实施方式中,人白蛋白融合蛋白的序列为:

[0326] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGRG-(GGGGS)$_m$-X_{IL0}RPSGRKSSKMQAFRIWDVNQK TFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKR FAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_n$-DAHKSEVAHRF KDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEM ADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKA AFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLT KVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV CKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQN CELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT

PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL,其中,m、n分别是0、1、2、3、4、5或6;其它变量如上文中所定义的。

[0327] 在一个实施方式中,人白蛋白融合蛋白的序列为:

[0328] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGRHX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGR-$(GGGGS)_m$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE-$(GGGGS)_n$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL,其中,m、n分别是0、1、2、3、4、5或6;其它变量如上文中所定义的。

[0329] 在一个实施方式中,人白蛋白融合蛋白的序列为:

[0330] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGRHX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGR-$(GGGGS)_m$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL,其中,m、n分别是0、1、2、3、4、5或6;其它变量如上文中所定义的。

[0331] 在一个实施方式中,人白蛋白融合蛋白的序列为:

[0332] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGG$(PSSGAPPPS)_{t2}$HGEGTFTSDLSKQMEEEAVRLFIEWLKNGG$(PSSGAPPPS)_{t2}$-$(GGGGS)_m$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE-$(GGGGS)_n$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVST

PTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDET YVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEG KKLVAASQAALGL,其中,m、n分别是0、1、2、3、4、5或6;t2是0或1。

[0333] 在一个实施方式中,人白蛋白融合蛋白的序列为:

[0334] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGG(PSSGAPPPS)$_{t2}$HGEGTFTSDLSKQMEEEAVRLFIEWL KNGG(PSSGAPPPS)$_{t2}$-(GGGGS)$_m$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFA KTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTA FHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCAS LQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKEC CEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYE TTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNL GKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAET FTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAA LGL-(GGGGS)$_n$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGG KMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDE GVMVTKFYFQEDE,其中,m、n分别是0、1、2、3、4、5或6;t2是0或1。

[0335] 在一个实施方式中,IgG1 Fc融合蛋白的序列为

[0336] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-(GGGGS)$_m$-X_{IL0}RPSGRKSSKMQAFRIW DVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENR KQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_n$-AEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK, 其中,其中,m、n分别是0、1、2、3、4、5或6;X_{IL0}是甲硫氨酸、半胱氨酸、通式1、通式2或缺失。

[0337] 在一个实施方式中,IgG1 Fc融合蛋白的序列为

[0338] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-(GGGGS)$_m$-AEPKSCDKTHTCPPCPAPE LLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK-(GGGGS)$_n$-X_{IL0}R PSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETR LQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE, 其中,m、n分别是0、1、2、3、4、5或6;X_{IL0}是甲硫氨酸、半胱氨酸、通式1、通式2或缺失。

[0339] 在一个实施方式中,IgG1 Fc融合蛋白的序列为:

[0340] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGRG-(GGGGS)$_m$-X_{IL0}RPSGRKSSKMQAFRIWDVNQK TFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKR FAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_n$-AEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK,其中,

m、n分别是0、1、2、3、4、5或6;其它变量分别如上文中所定义的。

[0341] 在一个实施方式中,IgG1 Fc融合蛋白的序列为:

[0342] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGRG-$(GGGGS)_m$-AEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK-$(GGGGS)_n$-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE,其中m、n分别是0、1、2、3、4、5或6;其它变量分别如上文中所定义的。

[0343] 二聚蛋白是由两个相同上述序列组成的同型二聚体,通过两个单体蛋白的Fc部分的半胱氨酸形成的链间二硫键。

[0344] 在一个实施方式中,IgG4 Fc与白介素-1受体拮抗蛋白的融合蛋白单体的序列为:

[0345] HX_{G2}EGTFTSDVSSYLEEQAAKEFIAWLVKGGG-$(GGGGS)_m$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE-$(GGGGS)_n$-AESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTC$_a$VVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC$_a$KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTC$_b$LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSC$_b$SVMHEALHNHYTQKSLSLSLG,其中m、n分别是0、1、2、3、4、5或6;其它变量如上文中所定义的。

[0346] 二聚蛋白是由两个相同上述序列组成的同型二聚体。每个加下划线的半胱氨酸C与另外一个单体对应位置的半胱氨酸形成链间二硫键;每个单体的C_a之间形成链间二硫键;每个单体的C_b之间形成链间二硫键。

[0347] 在一个实施方式中,IgG4 Fc与白介素-1受体拮抗蛋白的融合蛋白单体的序列为:

[0348] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGG-$(PSSGAPPPS)_{t2}$-$(GGGGS)_m$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE-$(GGGGS)_n$-AESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTC$_a$VVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC$_a$KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTC$_b$LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSC$_b$SVMHEALHNHYTQKSLSLSLG,其中,m、n分别是0、1、2、3、4、5或6;其它变量如上文中所定义的。

[0349] 二聚蛋白是由两个相同上述序列组成的同型二聚体。每个加下划线的半胱氨酸C与另外一个单体对应位置的半胱氨酸形成链间二硫键;每个单体的C_a之间形成链间二硫键;每个单体的C_b之间形成链间二硫键。

[0350] (2)白介素-1受体拮抗蛋白-连接基或间隔基-GLP-1受体结合多肽的融合蛋白

[0351] 白介素-1受体拮抗蛋白可以利用116位的半胱氨酸或在0(或N末端)、6、8、9、84、141、153(或C末端)引入半胱氨酸,通过连接基(或间隔基)交联GLP-1受体结合多肽。

[0352] 在一个实施方式中,融合蛋白的序列为:

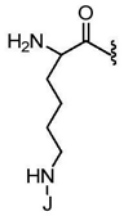
[0353] U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(连接基-GLP-1受体结合多

肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；

[0354] 在另一个实施方式中，融合蛋白的序列为：

[0355] U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(连接基-GLP-1受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；

[0356] 其中，U_L是-W-X-Y-Z结构、脂肪酸、聚乙二醇、白蛋白、IgG Fc、糖基团、氢原子或N^{α}-(N^{α}-(HOOC$(CH_2)_n$CO)-γ-Glu)-、N^{α}-(N^{α}-($CH_3(CH_2)_n$CO)-γ-Glu)-，其中n是整数8-20，如10、12、14、16、18或20，N^{α}表示氨基酸或氨基酸残基的α-氨基，或为通式5；其它变量分别如上文中所定义的。通式5结构是：

[0357] 

[0358] 在一个具体的实施方式中，连接基的分子结构可以是马来酰亚胺-PEG-马来酰亚胺或I-CH_2-CONH-PEG-NHCO-CH_2-I；在一个具体的实施方式中，连接基的分子结构可以是马来酰亚胺-$(CH_2)_n$-马来酰亚胺或I-CH_2-CONH-$(CH_2)_n$-NHCO-CH_2-I，其中n可以是1至30的整数；在一个具体的实施方式中，连接基的分子结构可以是马来酰亚胺-PEG-NHS。GLP-1受体结合多肽一般可以通过氨基酸残基侧链的氨基或巯基与连接基反应。

[0359] 在一个实施方式中，GLP-1受体结合多肽序列可以是：

[0360] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QX_{E14}EEEAVX_{E20}LFIEWL$X_{E27}X_{E28}X_{E29}X_{E30}$($PX_{E32}X_{E33}GX_{E35}$PPPC)$_{t2}$；

[0361] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QX_{E14}EEEAVX_{E20}LFIEWL$X_{E27}X_{E28}X_{E29}X_{E30}$($PX_{E32}X_{E33}$GCPPP$X_{E39}$)$_{t2}$；

[0362] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QX_{E14}EEEAVX_{E20}LFIEWL$X_{E27}X_{E28}X_{E29}X_{E30}$($PX_{E32}CGX_{E35}PPPX_{E39}$)$_{t2}$；

[0363] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QX_{E14}EEEAVX_{E20}LFIEWL$X_{E27}X_{E28}X_{E29}X_{E30}$(PC$X_{E33}GX_{E35}PPPX_{E39}$)$_{t2}$；

[0364] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QX_{E14}EEEAVX_{E20}LFIEWL$X_{E27}X_{E28}X_{E29}$C($PX_{E32}X_{E33}GX_{E35}$PPPX_{E39})$_{t2}$；

[0365] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QX_{E14}EEEAVX_{E20}LFIEWL$X_{E27}X_{E28}$CX_{E30}($PX_{E32}X_{E33}GX_{E35}$PPPX_{E39})$_{t2}$；

[0366] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QX_{E14}EEEAVX_{E20}LFIEWLX_{E27}C$X_{E29}X_{E30}$($PX_{E32}X_{E33}GX_{E35}$PPPX_{E39})$_{t2}$；

[0367] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QX_{E14}EEEAVX_{E20}LFIEWLC$X_{E28}X_{E29}X_{E30}$($PX_{E32}X_{E33}GX_{E35}$PPPX_{E39})$_{t2}$；

[0368] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QX_{E14}EEEAVCLFIEWL$X_{E27}X_{E28}X_{E29}X_{E30}$($PX_{E32}X_{E33}GX_{E35}PPPX_{E39}$)$_{t2}$；

[0369] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QCEEEAVX_{E20}LFIEWL$X_{E27}X_{E28}X_{E29}X_{E30}$($PX_{E32}X_{E33}GX_{E35}PPPX_{E39}$)$_{t2}$；

[0370] $X_{E1}X_{E2}$EGTFTSDX_{E10}SCQX_{E14}EEEAVX_{E20}LFIEWL$X_{E27}X_{E28}X_{E29}X_{E30}$($PX_{E32}X_{E33}GX_{E35}PPPX_{E39}$)$_{t2}$；

[0371] $X_{E1}X_{E2}$EGTFTSDCSX_{E12}QX_{E14}EEEAVX_{E20}LFIEWL$X_{E27}X_{E28}X_{E29}X_{E30}$($PX_{E32}X_{E33}GX_{E35}PPPX_{E39}$)$_{t2}$；

各序列中的各变量分别如上文中所定义的。

[0372] 在一个具体的实施方式中，GLP-1受体结合多肽序列可以是下述序列之一：

[0373] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSC；

[0374] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPC；

[0375] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGCPPPS；

[0376] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSCGAPPPS；

[0377] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPCSGAPPPS；

[0378] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGCPSSGAPPPS;

[0379] HGEGTFTSDLSKQMEEEAVRLFIEWLKNCGPSSGAPPPS;

[0380] HGEGTFTSDLSKQMEEEAVRLFIEWLKCGGPSSGAPPPS;

[0381] HGEGTFTSDLSKQMEEEAVRLFIEWLCNGGPSSGAPPPS;

[0382] HGEGTFTSDLSKQMEEEAVRLFIECLKNGGPSSGAPPPS;

[0383] HGEGTFTSDLSKQMEEEAVCLFIEWLKNGGPSSGAPPPS;

[0384] HGEGTFTSDLSKQCEEEAVRLFIEWLKNGGPSSGAPPPS;

[0385] HGEGTFTSDLSCQMEEEAVRLFIEWLKNGGPSSGAPPPS;

[0386] HGEGTFTSDCSKQMEEEAVRLFIEWLKNGGPSSGAPPPS;

[0387] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGC。

[0388] GLP-1受体结合多肽通过半胱氨酸侧链的巯基与连接基上的马来酰亚胺或碘代乙酰基反应,连接到白介素-1受体拮抗蛋白;

[0389] 在一个实施方式中,GLP-1受体结合多肽序列可以是:

[0390] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QX_{E14}EEEAVX_{E20}LFIEWL$X_{E27}X_{E28}X_{E29}X_{E30}$(P$X_{E32}X_{E33}GX_{E35}$PPPK)$_{t2}$;

[0391] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QX_{E14}EEEAVX_{E20}LFIEWL$X_{E27}X_{E28}X_{E29}X_{E30}$(P$X_{E32}X_{E33}$GKPPP$X_{E39}$)$_{t2}$;

[0392] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QX_{E14}EEEAVX_{E20}LFIEWL$X_{E27}X_{E28}X_{E29}X_{E30}$(P$X_{E32}KGX_{E35}PPPX_{E39}$)$_{t2}$;

[0393] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QX_{E14}EEEAVX_{E20}LFIEWL$X_{E27}X_{E28}X_{E29}X_{E30}$(PK$X_{E33}GX_{E35}PPPX_{E39}$)$_{t2}$;

[0394] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QX_{E14}EEEAVX_{E20}LFIEWL$X_{E27}X_{E28}X_{E29}$K(P$X_{E32}X_{E33}$GX_{E35}PPPX_{E39})$_{t2}$;

[0395] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QX_{E14}EEEAVX_{E20}LFIEWL$X_{E27}X_{E28}$KX_{E30}(P$X_{E32}X_{E33}$GX_{E35}PPPX_{E39})$_{t2}$;

[0396] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QX_{E14}EEEAVX_{E20}LFIEWLX_{E27}K$X_{E29}X_{E30}$(P$X_{E32}X_{E33}$GX_{E35}PPPX_{E39})$_{t2}$;

[0397] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QX_{E14}EEEAVX_{E20}LFIEWLK$X_{E28}X_{E29}X_{E30}$(P$X_{E32}X_{E33}$GX_{E35}PPPX_{E39})$_{t2}$;

[0398] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QX_{E14}EEEAVKLFIEWL$X_{E27}X_{E28}X_{E29}X_{E30}$(P$X_{E32}X_{E33}GX_{E35}PPPX_{E39}$)$_{t2}$;

[0399] $X_{E1}X_{E2}$EGTFTSDX_{E10}SX_{E12}QKEEEAVX_{E20}LFIEWL$X_{E27}X_{E28}X_{E29}X_{E30}$(P$X_{E32}X_{E33}GX_{E35}PPPX_{E39}$)$_{t2}$;

[0400] $X_{E1}X_{E2}$EGTFTSDX_{E10}SKQX_{E14}EEEAVX_{E20}LFIEWL$X_{E27}X_{E28}X_{E29}X_{E30}$(P$X_{E32}X_{E33}GX_{E35}PPPX_{E39}$)$_{t2}$;

[0401] $X_{E1}X_{E2}$EGTFTSDKSX_{E12}QX_{E14}EEEAVX_{E20}LFIEWL$X_{E27}X_{E28}X_{E29}X_{E30}$(P$X_{E32}X_{E33}GX_{E35}PPPX_{E39}$)$_{t2}$;

各序列中的各变量分别如上文中所定义的。

[0402] 在一个具体的实施方式中,GLP-1受体结合多肽序列可以是下述序列之一:

[0403] HGEGTFTSDLSRQMEEEAVRLFIEWLRNGGPSSGAPPPSK;

[0404] HGEGTFTSDLSRQMEEEAVRLFIEWLRNGGPSSGAPPPK;

[0405] HGEGTFTSDLSRQMEEEAVRLFIEWLRNGGPSSGKPPPS;

[0406] HGEGTFTSDLSRQMEEEAVRLFIEWLRNGGPSKGAPPPS;

[0407] HGEGTFTSDLSRQMEEEAVRLFIEWLRNGGPKSGAPPPS;

[0408] HGEGTFTSDLSRQMEEEAVRLFIEWLRNGKPSSGAPPPS;

[0409] HGEGTFTSDLSRQMEEEAVRLFIEWLRNKGPSSGAPPPS;

[0410] HGEGTFTSDLSRQMEEEAVRLFIEWLRKGGPSSGAPPPS;

[0411] HGEGTFTSDLSRQMEEEAVRLFIEWLKNGGPSSGAPPPS;

[0412] HGEGTFTSDLSRQMEEEAVRLFIEKLRNGGPSSGAPPPS;

[0413] HGEGTFTSDLSRQMEEEAVKLFIEWLRNGGPSSGAPPPS;

[0414] HGEGTFTSDLSRQKEEEAVRLFIEWLRNGGPSSGAPPPS;

[0415] HGEGTFTSDLSKQMEEEAVRLFIEWLRNGGPSSGAPPPS；

[0416] HGEGTFTSDKSRQMEEEAVRLFIEWLRNGGPSSGAPPPS；

[0417] HGEGTFTSDLSRQMEEEAVRLFIEWLRNGK-NH_2。

[0418] GLP-1受体结合多肽通过赖氨酸侧链的氨基与连接基的N-羟基琥珀酰亚胺酯反应，进而连接到白介素-1受体拮抗蛋白；

[0419] 在一个实施方式中，GLP-1受体结合多肽序列可以是：

[0420] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLV$X_{G28}X_{G29}X_{G30}$($PX_{E32}X_{E33}GX_{E35}$PPPC)$_{t2}$；

[0421] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLV$X_{G28}X_{G29}X_{G30}$($PX_{E32}X_{E33}$GCPPPX_{E39})$_{t2}$；

[0422] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLV$X_{G28}X_{G29}X_{G30}$(PX_{E32}CGX_{E35}PPPX_{E39})$_{t2}$；

[0423] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLV$X_{G28}X_{G29}X_{G30}$($PCX_{E33}GX_{E35}$PPPX_{E39})$_{t2}$；

[0424] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLV$X_{G28}X_{G29}X_{G30}$C；

[0425] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLV$X_{G28}X_{G29}$C-NH_2；

[0426] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLVX_{G28}C$X_{G30}X_{G31}$；

[0427] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLVC$X_{G29}X_{G30}X_{G31}$；

[0428] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIACLV$X_{G28}X_{G29}X_{G30}X_{G31}$；

[0429] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAACEFIAWLV$X_{G28}X_{G29}X_{G30}X_{G31}$；

[0430] $X_{G1}X_{G2}$EGTFTSDX_{G10}SCYLEX_{G16}QAAX_{G20}EFIAWLV$X_{G28}X_{G29}X_{G30}X_{G31}$；

[0431] $X_{G1}X_{G2}$EGTFTSDCSX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLV$X_{G28}X_{G29}X_{G30}X_{G31}$；

[0432] 各序列中的各变量分别如上文中所定义的。

[0433] 在一个具体的实施方式中，GLP-1受体结合多肽可以是以下序列之一：

[0434] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGRPSSGAPPPC；

[0435] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGRPSSGCPPPS；

[0436] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGRPSCGAPPPS；

[0437] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGRPCSGAPPPS；

[0438] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGRC；

[0439] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKGC-NH_2；

[0440] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVKCRG；

[0441] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVCGRG；

[0442] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVCGR-NH_2；

[0443] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIACLVKGRG；

[0444] HX_{G2}EGTFTSDVSSYLEX_{G16}QAACEFIAWLVKGRG；

[0445] HX_{G2}EGTFTSDVSSYLEX_{G16}QAACEFIAWLVKGR-NH_2；

[0446] HX_{G2}EGTFTSDVSCYLEX_{G16}QAAKEFIAWLVKGRG；

[0447] HX_{G2}EGTFTSDCSSYLEX_{G16}QAAKEFIAWLVKGRG；

[0448] HX_{G2}EGTFTSDCSSYLEX_{G16}QAAKEFIAWLVKGR-NH_2；

[0449] 各序列中的各变量分别如上文中所定义的。

[0450] 多肽通过半胱氨酸侧链的巯基与连接基一端的马来酰亚胺或碘代乙酰基反应，进而连接到白介素-1受体拮抗蛋白。

[0451] 在一个实施方式中，GLP-1受体结合多肽序列可以是：

[0452] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLV$X_{G28}X_{G29}X_{G30}$(P$X_{E32}X_{E33}$GX_{E35}PPPK)$_{t2}$;

[0453] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLV$X_{G28}X_{G29}X_{G30}$(P$X_{E32}X_{E33}$GKPPPX_{E39})$_{t2}$;

[0454] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLV$X_{G28}X_{G29}X_{G30}$(PX_{E32}KGX_{E35}PPPX_{E39})$_{t2}$;

[0455] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLV$X_{G28}X_{G29}X_{G30}$(PKX_{E33}GX_{E35}PPPX_{E39})$_{t2}$;

[0456] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLV$X_{G28}X_{G29}X_{G30}$K;

[0457] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLV$X_{G28}X_{G29}$K-NH_2;

[0458] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLVX_{G28}K$X_{G30}X_{G31}$;

[0459] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLVK$X_{G29}X_{G30}X_{G31}$;

[0460] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAX_{G20}EFIAKLV$X_{G28}X_{G29}X_{G30}X_{G31}$;

[0461] $X_{G1}X_{G2}$EGTFTSDX_{G10}SX_{G12}YLEX_{G16}QAAKEFIAWLV$X_{G28}X_{G29}X_{G30}X_{G31}$;

[0462] $X_{G1}X_{G2}$EGTFTSDX_{G10}SKYLEX_{G16}QAAX_{G20}EFIAWLV$X_{G28}X_{G29}X_{G30}X_{G31}$;

[0463] $X_{G1}X_{G2}$EGTFTSDKSX_{G12}YLEX_{G16}QAAX_{G20}EFIAWLV$X_{G28}X_{G29}X_{G30}X_{G31}$;和

[0464] 各序列中的各变量分别如上文中所定义的。

[0465] 在一个具体的实施方式中,GLP-1受体结合多肽可以是以下序列之一:

[0466] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAREFIAWLVRGRPSSGAPPPK;

[0467] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAREFIAWLVRGRPSSGKPPPS;

[0468] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAREFIAWLVRGRPSKGAPPPS;

[0469] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAREFIAWLVRGRPKSGAPPPS;

[0470] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAREFIAWLVRGRK;

[0471] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAREFIAWLVRGK-NH_2;

[0472] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAREFIAWLVRKRG;

[0473] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAREFIAWLVKGRG;

[0474] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAREFIAKLVRGRG;

[0475] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVRGRG;

[0476] HX_{G2}EGTFTSDVSSYLEX_{G16}QAAKEFIAWLVRGR-NH_2;

[0477] HX_{G2}EGTFTSDVSKYLEX_{G16}QAAREFIAWLVRGRG;

[0478] HX_{G2}EGTFTSDKSSYLEX_{G16}QAAREFIAWLVRGRG;和

[0479] HX_{G2}EGTFTSDKSSYLEX_{G16}QAAREFIAWLVRGR-NH_2;

[0480] 各序列中的各变量分别如上文中所定义的。

[0481] GLP-1受体结合多肽通过赖氨酸侧链的氨基与连接基的N-羟基琥珀酰亚胺酯反应,进而连接到白介素-1受体拮抗蛋白。

[0482] 在一个实施方式中,融合蛋白的序列为:

[0483] (GLP-1受体结合多肽-连接基)-C_{IL0}-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者,

[0484] C_{IL0}(连接基-GLP-1受体结合多肽)X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者,

[0485] U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHG

GKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDEC$_{IL153}$(连接基-GLP-1受体结合多肽)，其中，

[0486] C$_{IL0}$、C$_{IL153}$是半胱氨酸或缺失；其它变量分别如上文中所定义的。连接基如本文所定义。在一种实施方式中，连接基有一个醛基，通过还原性胺化(reductive amination)与白介素-1受体拮抗蛋白N末端连接；在另外一种实施方式中，C$_{IL0}$半胱氨酸通过侧链巯基与连接基连接，再连接GLP-1受体结合多肽。

[0487] GLP-1受体结合多肽一般可以通过氨基酸残基侧链的氨基或巯基与连接基反应。

[0488] 在一种实施方式中，GLP-1受体结合多肽是经过修饰的缀合物。GLP-1受体结合多肽与白介素-1受体拮抗蛋白的融合蛋白/二聚蛋白/交联蛋白的序列选自：

[0489] G-1：

[0490] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；(SEQ ID NO:1)

[0491] G-2：

[0492] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；(SEQ ID NO:2)

[0493] G-3：

[0494] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；(SEQ ID NO:3)

[0495] G-4：

[0496] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；(SEQ ID NO:4)

[0497] G-5：

[0498] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；(SEQ ID NO:5)

[0499] G-6：

[0500] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；(SEQ ID NO:6)

[0501] G-7：

[0502] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；(SEQ ID NO:7)

[0503] G-8：

[0504] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGGGSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYL

RNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFI RSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:8)

[0505] G-9：

[0506] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGSRPSGRKSSKMQAFRIWDVNQKTFY LRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAF IRSDSGPTTSFESAAC[S-马来酰亚胺-$(CH_2)_4$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]PGWFLCTAME ADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子);(SEQ ID NO:9)

[0507] G-10：

[0508] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGSRPSGRKSSKMQAFRIWDVNQKTFY LRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-CH_2-CONH-PEG20K)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子);(SEQ ID NO:10)

[0509] G-11：

[0510] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQ LVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDS GPTTSFESAAC(S-CH_2-CONH-PEG20K)PGWFLCTA MEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子);(SEQ ID NO:11)

[0511] G-12：

[0512] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVN QKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC[S-马来酰亚胺-$(CH_2)_4$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFL CTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子);(SEQ ID NO:12)

[0513] G-13：

[0514] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYL QGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSF ESAAC(S-马来酰亚胺-PEG20K)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子);(SEQ ID NO:13)

[0515] G-14：

[0516] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYL QGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC[S-马来酰亚胺-$(CH_2)_4$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAME ADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子);(SEQ ID NO:14)

[0517] G-15：

[0518] HGEGTFTSDLSKQMEEEAVRLFIEWLC[S-马来酰亚胺-$(CH_2)_4$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]NGGPSSGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKI DVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLC TAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子);(SEQ ID NO:15)

[0519] G-16：

[0520] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPC(S-CH_2-CONH-PEG20K)GGGGSGGGGS

RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDET RLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE (S是半胱氨酸侧链的硫原子)；(SEQ ID NO:16)

[0521] G-17：

[0522] HGEGTFTSDLSKQMEEEAVC[S-马来酰亚胺-$(CH_2)_4$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]LFIEWLKNGGPSSGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNL EEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPG WFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:17)

[0523] G-18：

[0524] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRGRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQG PNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFES AACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:18)

[0525] G-19：

[0526] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAG YLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTT SFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:19)

[0527] G-20：

[0528] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNN QLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSD SGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:20)

[0529] G-21：

[0530] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRGGGGSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTF YLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFA FIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:21)

[0531] G-22：

[0532] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRPSSGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVN QKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQD KRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:22)

[0533] G-23：

[0534] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRGRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQG PNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFES AAC(S-CH_2-CONH-PEG20K)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:23)

[0535] G-24：

[0536] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAG YLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTT SFESAAC(S-CH_2-CONH-PEG20K)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:24)

[0537] G-25：

[0538] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC[S-马来酰亚胺-$(CH_2)_4$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子);(SEQ ID NO:25)

[0539] G-26:

[0540] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-CH_2-CONH-PEG20K)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子);(SEQ ID NO:26)

[0541] G-27:

[0542] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC[S-马来酰亚胺-$(CH_2)_4$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子);(SEQ ID NO:27)

[0543] G-28:

[0544] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRGGGGSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-CH_2-CONH-PEG20K)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子);(SEQ ID NO:28)

[0545] G-29:

[0546] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRPSSGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC[S-马来酰亚胺-$(CH_2)_4$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子);(SEQ ID NO:29)

[0547] G-30:

[0548] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPC(S-马来酰亚胺-$(CH_2)_{15}$-COOH)GGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子);(SEQ ID NO:30)

[0549] G-31:

[0550] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPC(S-马来酰亚胺-$(CH_2)_{17}$-COOH)GGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子);(SEQ ID NO:31)

[0551] G-32:

[0552] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPC[S-CH_2-CONH-$(CH_2CH_2O)_2$-$(CH_2)_2$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]-GGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子);(SEQ ID

NO:32)

[0553] G-33：

[0554] HGEGTFTSDLSKQMEEEAVRLFIEWLC[S-CH_2-CONH-$(CH_2CH_2O)_2$-$(CH_2)_2$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]NGGPSSGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:33)

[0555] G-34：

[0556] HGEGTFTSDLSKQMEEEAVC[S-CH_2-CONH-$(CH_2CH_2O)_2$-$(CH_2)_2$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]LFIEWLKNGGPSSGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:34)

[0557] G-35：

[0558] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPC[S-CH_2-CONH-$(CH_2CH_2O)_2$-$(CH_2)_2$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]SGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:35)

[0559] G-36：

[0560] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-$(CH_2)_{15}$-COOH)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:36)

[0561] G-37：

[0562] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC[S-CH_2-CONH-$(CH_2CH_2O)_2$-$(CH_2)_2$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:37)

[0563] G-38：

[0564] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-$(CH_2)_{17}$-COOH)-PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:38)

[0565] G-39：

[0566] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC[S-CH_2-CONH-$(CH_2CH_2O)_4$-$(CH_2)_2$-NH-(N^{α}-(HOOC$(CH_2)_{16}$CO)-γ-

Glu)]-PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:39)

[0567] G-40：

[0568] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRC(S-马来酰亚胺-$(CH_2)_{15}$-COOH)GGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:40)

[0569] G-41：

[0570] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRC[S-CH_2-CONH-$(CH_2CH_2O)_2$-$(CH_2)_2$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]GGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:41)

[0571] G-42：

[0572] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-$(CH_2)_{17}$-COOH)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQID NO:42)

[0573] G-43：

[0574] HGEGTFTSDVSSYLEEQAAC[S-CH_2-CONH-$(CH_2CH_2O)_2$-$(CH_2)_2$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]EFIAWLVKGRGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:43)

[0575] G-44：

[0576] HAEGTFTSDVSSYLEGQAAC[S-CH_2-CONH-$(CH_2CH_2O)_2$-$(CH_2)_2$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]EFIAWLVKGRGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:44)

[0577] G-45：

[0578] HGEGTFTSDC[S-CH_2-CONH-$(CH_2CH_2O)_2$-$(CH_2)_2$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO-γ-Glu-N-γ-Glu)]SSYLEEQAAKEFIAWLVKGRGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:45)

[0579] G-46：

[0580] HAEGTFTSDC[S-CH_2-CONH-$(CH_2CH_2O)_2$-$(CH_2)_2$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]SSYLEGQAAKEFIAWLVKGRGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:46)

[0581] G-47：

[0582] HGEGTFTSDVSSYLEEQAAKEFIAWLVC[S-CH_2-CONH-$(CH_2CH_2O)_2$-$(CH_2)_2$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]GRGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子);(SEQ ID NO:47)

[0583] G-48:

[0584] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC[S-CH_2-CONH-$(CH_2CH_2O)_4$-$(CH_2)_2$-NH-(N^{α}-(HOOC$(CH_2)_{16}$CO)-γ-Glu)]ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子);(SEQ ID NO:48)

[0585] G-49:

[0586] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-$(CH_2)_{15}$-COOH)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子);(SEQ ID NO:49)

[0587] G-50:

[0588] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC[S-CH_2-CONH-$(CH_2CH_2O)_2$-$(CH_2)_2$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子);(SEQ ID NO:50)

[0589] G-51:

[0590] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子),(SEQ ID NO:51),其中GLP-1受体结合多肽的序列是:HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPC(SEQ ID NO:185),通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0591] G-52:

[0592] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:52),其中GLP-1受体结合多肽的序列是SEQ ID NO:185,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0593] G-53:

[0594] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:53),其中GLP-1受体结合多肽的序列是:HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRC(SEQ ID NO:186),通过末端半胱氨酸侧链巯基与马来

酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0595] G-54:

[0596] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFE SAAC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:54),其中GLP-1受体结合多肽的序列是SEQ ID NO:186,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0597] G-55:

[0598] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:55),其中GLP-1受体结合多肽的序列是:HGEGTFTSDVSSYLEEQAAKEFIAWLVCGRG(SEQ ID NO:187),通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0599] G-56:

[0600] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:56),其中GLP-1受体结合多肽的序列是SEQ ID NO:187,通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0601] G-57:

[0602] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:57),其中GLP-1受体结合多肽的序列是:HGEGTFTSDLSKQMEEEAVRLFIEWLCNGGPSSGAPPPS(SEQ ID NO:188),通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0603] G-58:

[0604] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:58),其中GLP-1受体结合多肽的序列是SEQ ID NO:188,通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0605] G-59:

[0606] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-PEG20K-马来酰亚胺-S-GLP-1受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTA MEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:59),其中GLP-1受体结合多肽的序列是SEQ ID NO:185,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0607] G-60：

[0608] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG20K-马来酰亚胺-S-GLP-1受体结合多肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:60)，其中GLP-1受体结合多肽的序列是SEQ ID NO:185，通过末端半胱氨酸侧链巯基与马来酰亚胺反应，连接白介素-1受体拮抗蛋白；

[0609] G-61：

[0610] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-PEG20K-马来酰亚胺-S-GLP-1受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTA MEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:61)，其中GLP-1受体结合多肽的序列是：HAibEGTFTSDVSSYLEGQAAKEFIAWLVKGRC(SEQ ID NO:189)，通过末端半胱氨酸侧链巯基与马来酰亚胺反应，连接白介素-1受体拮抗蛋白；

[0611] G-62：

[0612] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG20K-马来酰亚胺-S-GLP-1受体结合多肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:62)，其中GLP-1受体结合多肽的序列是SEQ ID NO:186，通过末端半胱氨酸侧链巯基与马来酰亚胺反应，连接白介素-1受体拮抗蛋白；

[0613] G-63：

[0614] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-PEG20K-马来酰亚胺-S-GLP-1受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:63)，其中GLP-1受体结合多肽的序列是SEQ ID NO:187，通过半胱氨酸侧链巯基与马来酰亚胺反应，连接白介素-1受体拮抗蛋白；

[0615] G-64：

[0616] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG20K-马来酰亚胺-S-GLP-1受体结合多肽)PGWFLCTA MEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:64)，其中GLP-1受体结合多肽的序列是：HAibEGTFTSDVSSYLEGQAAKEFIAWLVCGRG(SEQ ID NO:190)，通过半胱氨酸侧链巯基与马来酰亚胺反应，连接白介素-1受体拮抗蛋白；

[0617] G-65：

[0618] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-PEG20K-马来酰亚胺-S-GLP-1受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTA MEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:65)，其中GLP-1受体结合多肽的序列是SEQ ID NO:188，通过半胱氨酸侧链巯基与马来酰亚胺反应，连接白介素-1受体拮抗蛋白；

[0619] G-66：

[0620] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG20K-马来酰亚胺-S-GLP-1受体结合多肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:66),其中GLP-1受体结合多肽的序列是SEQ ID NO:188,通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0621] G-67:

[0622] (GLP-1受体结合多肽-S-马来酰亚胺-PEG20K-马来酰亚胺-S)CRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:67),其中GLP-1受体结合多肽的序列是SEQ ID NO:185,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0623] G-68:

[0624] (PEG20K)RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:68),其中GLP-1受体结合多肽的序列是SEQ ID NO:185,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0625] G-69:

[0626] (PEG20K)RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTA MEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:69),其中GLP-1受体结合多肽的序列是SEQ ID NO:186,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0627] G-70:

[0628] (GLP-1受体结合多肽-S-马来酰亚胺-PEG20K-马来酰亚胺-S)CRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:70),其中GLP-1受体结合多肽的序列是SEQ ID NO:189,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0629] G-71:

[0630] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:71),其中GLP-1受体结合多肽的序列是:HAibEGTFTSDVSSYLEEQAAKEFIAWLVKGRC(SEQ ID NO:191),通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0631] G-72:

[0632] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG11-马来酰亚

胺-S-GLP-1受体结合多肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:72),其中GLP-1受体结合多肽的序列是SEQ ID NO:191,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0633] G-73:

[0634] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:73),其中GLP-1受体结合多肽的序列是SEQ ID NO:189,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0635] G-74:

[0636] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:74),其中GLP-1受体结合多肽的序列是SEQ ID NO:189,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0637] G-75:

[0638] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:75),其中GLP-1受体结合多肽的序列是SEQ ID NO:190,通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0639] G-76:

[0640] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:76),其中GLP-1受体结合多肽的序列是SEQ ID NO:190,通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0641] G-77:

[0642] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:77),其中GLP-1受体结合多肽的序列是:HAibEGTFTSDVSSYLEGQAACEFIAWLVKGRG(SEQ ID NO:192),通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0643] G-78:

[0644] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:78),其中GLP-1受体结合多肽的序列是SEQ ID NO:192,通过半胱氨酸

侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0645] G-79:

[0646] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:79),其中GLP-1受体结合多肽的序列是:HAEGTFTSDVSSYLEGQAAK[N^{ε}-(N^{α}-(HOOC(CH_2)$_{14}$CO)-γ-L-Glu)]EFIAWLVRGRC(SEQ ID NO:193),通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0647] G-80:

[0648] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:80),其中GLP-1受体结合多肽的序列是SEQ ID NO:193,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;

[0649] G-81:

[0650] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGSGGGGSDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGLGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:81)

[0651] G-82:

[0652] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRPSSGAPPPSGGGGSGGGGSDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGLGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:82)

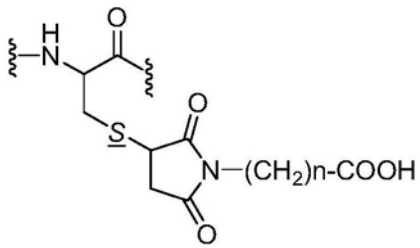
[0653] G-83:

[0654] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVN QKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQD KRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDEGGGGSGGGGSDAHKSEVAH RFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYG EMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRY KAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTD LTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIK QNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHE KTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATK EQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL;(SEQ ID NO:83)

[0655] G-84：

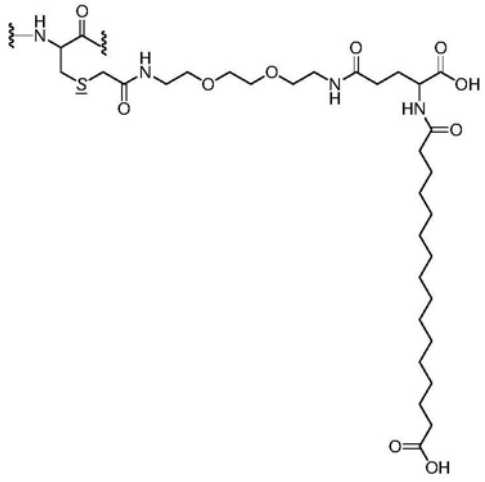
[0656] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRPSSGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVN QKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQD KRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDEGGGGSGGGGSDAHKSEVAH RFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYG EMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRY KAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTD LTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIK QNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHE KTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATK EQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL;(SEQ ID NO:84)

[0657] 本部分序列中C(S-马来酰亚胺-$(CH_2)_n$-COOH)的结构如下所示，

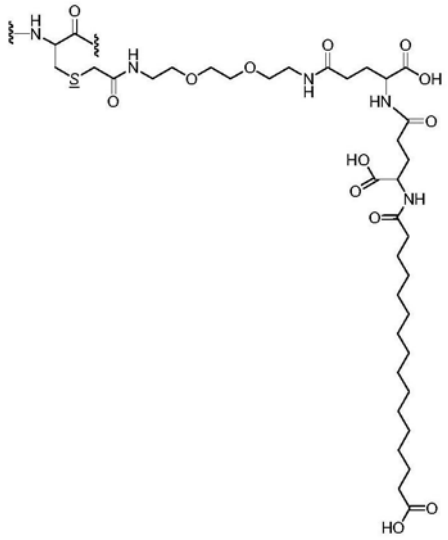
[0658] 

[0659] 其中，n是1-25的整数。

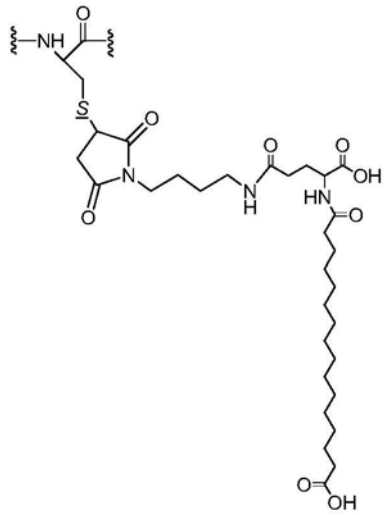
[0660] 本部分序列中C[S-CH_2-CONH-$(CH_2CH_2O)_2$-$(CH_2)_2$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]的结构如下所示：

[0661] 

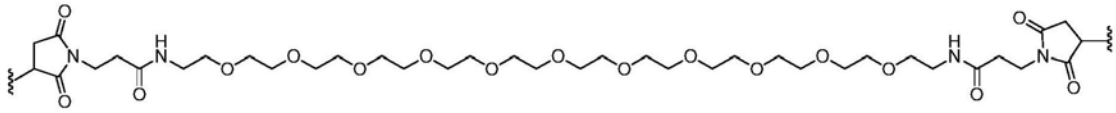
[0662] 本部分序列中C[S-CH_2-CONH-$(CH_2CH_2O)_2$-$(CH_2)_2$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu-N-γ-Glu)]的结构如下所示：

[0663] 

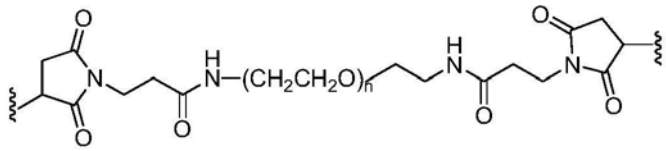
[0664] 本部分序列中C[S-马来酰亚胺-$(CH_2)_4$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]的结构如下所示：

[0665] 

[0666] 本部分序列中马来酰亚胺-PEG11-马来酰亚胺的结构如下所示：

[0667] 

[0668] 本部分序列中马来酰亚胺-PEG20K-马来酰亚胺的结构如下所示：

[0669]  其中n是0-2000的整数。

[0670] 2、胰岛素受体结合多肽与白介素-1受体拮抗蛋白的融合蛋白

[0671] 胰岛素受体结合多肽包括A链和B链，其中，

[0672] A链的氨基酸序列为：GIVEQC$_{[3]}$C$_{[4]}$X$_{IN8}$SIC$_{[5]}$SLYQLENYC$_{[6]}$X$_{IN21}$X$_{IN22}$或

[0673] GIVEQC$_{[3]}$C$_{[4]}$TSIC$_{[5]}$SLYQLENYC$_{[6]}$N；

[0674] B链氨基酸序列为：

[0675] X$_{IN23-26}$HLC$_{[1]}$GSHLVEALYLVC$_{[2]}$GERGFX$_{IN47}$X$_{IN48}$X$_{IN49}$X$_{IN50}$X$_{IN51}$X$_{IN52}$，其中，

[0676] X$_{IN8}$是苏氨酸、组氨酸或精氨酸；X$_{IN21}$是丙氨酸、甘氨酸或天冬酰胺；X$_{IN22}$是赖氨酸、精氨酸-赖氨酸二肽或缺失；X$_{IN23-26}$是苯丙氨酸-缬氨酸-天冬酰胺-谷氨酰胺四肽、缬氨酸-天冬酰胺-谷氨酰胺三肽、天冬酰胺-谷氨酰胺二肽、谷氨酰胺或缺失；X$_{IN47}$是酪氨酸或苯丙氨酸；X$_{IN48}$是-NH$_2$、dA-NH$_2$、酪氨酸或苯丙氨酸；X$_{IN49}$是苏氨酸、天冬酰胺或缺失；X$_{IN50}$是赖氨酸、脯氨酸、谷氨酸、天冬氨酸或缺失；X$_{IN51}$是脯氨酸、精氨酸、赖氨酸、谷氨酸、天冬氨酸或缺失；X$_{IN52}$是苏氨酸、苏氨酸-精氨酸-精氨酸或缺失；

[0677] 所述化合物中，[1]-[6]表示半胱氨酸的编号；所述化合物中通过6个半胱氨酸形成3对二硫键，其中A链和B链通过两对链间二硫键连接，A链内存在一对链内二硫键，三对二硫键的具体位置是：C$_{[1]}$和C$_{[4]}$形成二硫键，C$_{[2]}$和C$_{[6]}$形成二硫键，C$_{[3]}$和C$_{[5]}$形成二硫键。

[0678] 在另一种实施方式中，单链胰岛素受体结合多肽的氨基酸序列结构为：

[0679] X$_{IN107}$HLC$_{[1]}$GSX$_{IN108}$LVEALYLVC$_{[2]}$GEX$_{IN109}$GFX$_{IN110}$X$_{IN111}$X$_{IN112}$X$_{IN113}$X$_{IN114}$X$_{IN115}$-C$_L$-GIVEQC$_{[3]}$C$_{[4]}$X$_{IN127}$SIC$_{[5]}$SLYQLENYC$_{[6]}$X$_{IN128}$X$_{IN129}$，其中，

[0680] X$_{IN107}$是苯丙氨酸-缬氨酸-天冬酰胺-谷氨酰胺四肽、缬氨酸-天冬酰胺-谷氨酰胺三肽、天冬酰胺-谷氨酰胺二肽、或谷氨酰胺，或是以赖氨酸或精氨酸取代二、三、四肽序列中任何一个氨基酸残基后的序列，或缺失；X$_{IN108}$是组氨酸、苯丙氨酸、精氨酸或谷氨酰胺；X$_{IN109}$是精氨酸、丙氨酸、谷氨酸或天冬氨酸；X$_{IN110}$是苯丙氨酸、酪氨酸或组氨酸；X$_{IN111}$是酪氨酸、苯丙氨酸或缺失；X$_{IN112}$是苏氨酸、天冬酰胺或缺失；X$_{IN113}$是脯氨酸、赖氨酸、谷氨酸、天冬氨酸或缺失；X$_{IN114}$是赖氨酸、脯氨酸、精氨酸、谷氨酸、天冬氨酸或缺失；X$_{IN115}$是苏氨酸或缺失；X$_{IN127}$是苏氨酸、组氨酸或精氨酸；X$_{IN128}$是丙氨酸、甘氨酸或天冬酰胺；X$_{IN129}$是赖氨酸、精氨酸-赖氨酸二肽或缺失；C$_L$是6-60个氨基酸的肽序列，其中氨基酸主要选自由甘氨酸、丙氨酸、丝氨酸、苏氨酸、脯氨酸组成的组。

[0681] 适用的连接片段C$_L$具有三点特征：第一，连接片段需要适当的长度。当B链为30个氨基酸全长时，连接片段长度最好不少于6个氨基酸；当B链为25个氨基酸时，连接片段长度最好不少于10个氨基酸。连接片段长度过长或过短(短于上述氨基酸数目，或者长于60个氨基酸)时，单链类似物的胰岛素受体结合能力有降低趋势。第二，连接片段最好没有二级结构，空间构象可以灵活变化。第三，连接片段本身没有生物活性，但可以提供多肽修饰位点，

如酰化、糖基化等。

[0682] 该连接片段C_L可以包含1个或1个以上天冬氨酸、谷氨酸、精氨酸、赖氨酸、半胱氨酸或天冬酰胺。C_L可以包括1、2、3、4个天冬氨酸、谷氨酸、精氨酸或赖氨酸以调节多肽序列的电荷平衡，改善溶解度。该序列可以包括1、2、3、4、5个天冬酰胺和相同数量的丝氨酸或苏氨酸，从而组成构成N糖基化所需的N-X-S/T共有序列(X为可编码的天然氨基酸)。进一步地，该肽还可以包含1、2、3或4个赖氨酸或半胱氨酸，其侧链氨基或巯基可以与脂肪酸、聚乙二醇、白蛋白等天然或合成的修饰基团通过水解键或非水解键相连，从而使修饰后的胰岛素类似物具有不同的物理、化学和生物特性。

[0683] 根据一种实施方式，C_L的C末端氨基酸可以选自由甘氨酸-赖氨酸、甘氨酸-精氨酸、精氨酸-精氨酸、赖氨酸-赖氨酸、精氨酸-赖氨酸、赖氨酸-精氨酸、脯氨酸-谷氨酰胺-苏氨酸、脯氨酸-谷氨酰胺-赖氨酸、或脯氨酸-谷氨酰胺-精氨酸组成的组。根据一种实施方式，C_L的C末端氨基酸选自赖氨酸或精氨酸。

[0684] 在一种实施方式中，C_L是$GX_{IN116}X_{IN117}X_{IN118}X_{IN119}X_{IN120}X_{IN121}X_{IN122}X_{IN123}X_{IN124}X_{IN125}X_{IN126}$，其中，

[0685] X_{IN116}是赖氨酸、半胱氨酸、丝氨酸或丙氨酸；X_{IN117}是甘氨酸、赖氨酸或丝氨酸；X_{IN118}是赖氨酸或丝氨酸；X_{IN119}是赖氨酸或丝氨酸；X_{IN120}是赖氨酸、丝氨酸或丙氨酸；X_{IN121}是甘氨酸、赖氨酸、精氨酸、丙氨酸或脯氨酸或缺失；X_{IN122}是甘氨酸、丙氨酸、精氨酸、赖氨酸、谷氨酰胺或脯氨酸或缺失；X_{IN123}是精氨酸、赖氨酸、甘氨酸、丙氨酸、脯氨酸、苏氨酸或谷氨酰胺或缺失；X_{IN124}是脯氨酸、谷氨酰胺、赖氨酸、甘氨酸、精氨酸或缺失；X_{IN125}是谷氨酰胺、苏氨酸、赖氨酸、甘氨酸、精氨酸或缺失；X_{IN126}是苏氨酸、精氨酸、赖氨酸或缺失；

[0686] 在一个具体实施方式中，C_L可以是GAGSSSAAAPQT、GSGSSSAAAPQT、GSGSSSAAPQT、GSGSSSAPQT或GSGSSAPQT。

[0687] 在另一种实施方式中，单链胰岛素受体结合多肽的氨基酸序列结构为：

[0688] $FVNQHLC_{[1]}GSHLVEALYLVC_{[2]}GERGFFX_{IN111}X_{IN112}X_{IN113}X_{IN114}X_{IN115}-C_L-GIVEQC_{[3]}C_{[4]}TSIC_{[5]}SLYQLENYC_{[6]}N$，其中，各变量如上文中所定义的。

[0689] 本发明进一步提供一种在胰岛素受体结合多肽基础上进行修饰的化合物，以进一步提高所述化合物体内循环作用时间。所述修饰是将修饰侧链连接至本发明的双链化合物的B链的N-末端氨基酸残基的α-氨基或单链化合物的N-末端氨基酸残基的α-氨基，或者连接至本发明的双链或单链化合物中存在的赖氨酸的ε-氨基。

[0690] 在一种实施方式中，所述化合物包括A链和B链，其中，

[0691] A链的氨基酸序列为：

[0692] $GIVEQC_{[3]}C_{[4]}TSIC_{[5]}X_{IN412}LX_{IN414}X_{IN415}LX_{IN417}X_{IN418}YC_{[6]}X_{IN421}X_{IN422}$，

[0693] B链的氨基酸序列为：

[0694] $X_{IN423-426}HLC_{[1]}GSHLVEALYLVC_{[2]}GERGFX_{IN447}X_{IN448}X_{IN449}X_{IN450}X_{IN451}X_{IN452}X_{IN453}$，

[0695] 所述化合物中，[1]-[6]表示半胱氨酸的编号；所述化合物通过6个半胱氨酸形成3对二硫键，其中A链和B链通过两对链间二硫键连接，A链内存在一对链内二硫键，三对二硫键的具体位置是：$C_{[1]}$和$C_{[4]}$形成二硫键，$C_{[2]}$和$C_{[6]}$形成二硫键，$C_{[3]}$和$C_{[5]}$形成二硫键；

[0696] 其中X_{IN412}为丝氨酸或通式1结构：X_{IN414}为酪氨酸或通式1结构；X_{IN415}是谷氨酰胺或通式1结构；X_{IN417}为谷氨酸或通式1结构；X_{IN418}为天冬酰胺或通式1结构；X_{IN421}为是天冬酰

胺、丙氨酸或甘氨酸；X_{IN422}为赖氨酸、通式3、精氨酸-通式3或缺失；$X_{IN423-426}$是甘氨酸-脯氨酸-谷氨酸三肽、U_L-甘氨酸-脯氨酸-谷氨酸、苯丙氨酸-缬氨酸-天冬酰胺-谷氨酰胺四肽或U_L-苯丙氨酸-缬氨酸-天冬酰胺-谷氨酰胺；X_{IN447}是酪氨酸或苯丙氨酸；X_{IN448}是-NH_2、苯丙氨酸、酪氨酸或缺失；X_{IN449}是苏氨酸、天冬酰胺或缺失；X_{IN450}是赖氨酸、精氨酸、谷氨酸、天冬氨酸、脯氨酸或缺失；X_{IN451}是脯氨酸、赖氨酸、精氨酸、谷氨酸、天冬氨酸或缺失，或为通式1或通式3结构；X_{IN452}是苏氨酸、赖氨酸或缺失，或为通式1或通式3结构；X_{IN453}赖氨酸或缺失，或为通式3结构；U_L如本文所定义。

[0697] 在一种实施方式中，所述单链化合物的氨基酸序列结构为：

[0698] U_L-X_{IN300}HLC[1]GSHLVEALYLVC[2]GERGF$X_{IN301}X_{IN302}X_{IN303}X_{IN304}X_{IN305}X_{IN306}GX_{IN307}X_{IN308}X_{IN309}X_{IN310}X_{IN311}X_{IN312}X_{IN313}X_{IN314}X_{IN315}X_{IN316}X_{IN317}$GIVEQC[3]C[4]$X_{IN318}$SIC[5]$X_{IN319}LX_{IN320}X_{IN321}LX_{IN322}X_{IN323}$YC[6]$X_{IN324}X_{IN325}$，其中，

[0699] X_{IN300}是苯丙氨酸-缬氨酸-天冬酰胺-谷氨酰胺四肽、缬氨酸-天冬酰胺-谷氨酰胺三肽、天冬酰胺-谷氨酰胺二肽、谷氨酰胺、或是以赖氨酸或精氨酸取代二、三、四肽序列中任何一个氨基酸残基后的序列或缺失；X_{IN301}是苯丙氨酸、组氨酸或酪氨酸；X_{IN302}是-NH_2、酪氨酸、苯丙氨酸或缺失；X_{IN303}是苏氨酸、天冬酰胺或缺失；X_{IN304}是脯氨酸、赖氨酸、谷氨酸、天冬氨酸或缺失；X_{IN305}是天冬氨酸、谷氨酸、脯氨酸、精氨酸、赖氨酸、缺失或通式1结构；X_{IN306}是苏氨酸、通式1结构或缺失；X_{IN307}是丝氨酸、丙氨酸、甘氨酸、赖氨酸、通式1结构或缺失；X_{IN308}是甘氨酸、通式1结构或缺失；X_{IN309}是赖氨酸、甘氨酸、丝氨酸、通式1结构或缺失；X_{IN310}是赖氨酸、甘氨酸、丝氨酸、通式1结构或缺失；X_{IN311}是赖氨酸、甘氨酸、丝氨酸、丙氨酸、通式1结构或缺失；X_{IN312}是赖氨酸、精氨酸、丙氨酸、脯氨酸、甘氨酸、通式1结构或缺失；X_{IN313}是甘氨酸、丙氨酸、精氨酸、赖氨酸、谷氨酰胺、脯氨酸、通式1结构或缺失；X_{IN314}是精氨酸、丙氨酸、脯氨酸、苏氨酸、谷氨酰胺、甘氨酸、通式1结构或缺失；X_{IN315}是脯氨酸、谷氨酰胺、精氨酸、甘氨酸、缺失或通式I结构；X_{IN316}是谷氨酰胺、苏氨酸、精氨酸、甘氨酸、缺失或通式1结构；X_{IN317}是苏氨酸、精氨酸、赖氨酸或缺失；X_{IN318}是苏氨酸、组氨酸、精氨酸或通式1结构；X_{IN319}是丝氨酸或通式1结构；X_{IN320}是酪氨酸或通式1结构；X_{IN321}是谷氨酰胺或通式1结构；X_{IN322}是谷氨酸或通式1结构；X_{IN323}是天冬酰胺或通式1结构；X_{IN324}是天冬氨酸、甘氨酸、丙氨酸或通式1结构；X_{IN325}是赖氨酸、通式3、精氨酸-通式3或缺失；U_L和通式1、通式3结构如本文中所定义。

[0700] 在另一种实施方式中，所述化合物为另一种单链结构，氨基酸序列结构为：

[0701] U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFF$X_{IN302}X_{IN303}X_{IN304}X_{IN305}X_{IN306}GX_{IN307}X_{IN308}X_{IN309}X_{IN310}X_{IN311}X_{IN312}X_{IN313}X_{IN314}X_{IN315}X_{IN316}X_{IN317}$GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NX_{IN325}，其中，各变量如本文中所定义的。

[0702] 胰岛素受体结合多肽和白介素-1受体拮抗蛋白能够通过相似或不同的机理保护胰岛β细胞，治疗糖尿病。因此，将两种多肽连接后形成的融合蛋白可以通过两种多肽的协同作用，达到比单独使用其中一种多肽更优异的治疗效果。另外，胰岛素受体的主要分布组织及周边的炎症往往是糖尿病发病的原因之一。胰岛素受体结合多肽可以为融合蛋白起到靶向作用，使白介素-1受体拮抗蛋白富集于这些组织，更有效地发挥消炎等作用。

[0703] 胰岛素受体结合多肽和白介素-1受体拮抗蛋白通过可选的连接基(或间隔基)相连，有多种连接方式。

[0704] (1)胰岛素受体结合多肽与白介素-1受体拮抗蛋白的连接方式为(从左到右对应氨基酸序列从N末端到C末端)：

[0705] 胰岛素受体结合多肽-连接基(或间隔基)-白介素-1受体拮抗蛋白;或者

[0706] 白介素-1受体拮抗蛋白-连接基(或间隔基)-胰岛素受体结合多肽;

[0707] 在一个实施方式中,融合蛋白序列为：

[0708] U_L-X_{IN107}HLC[1]GSX$_{IN108}$LVEALYLVC[2]GEX$_{IN109}$GFX$_{IN110}$X$_{IN111}$X$_{IN112}$X$_{IN113}$X$_{IN114}$X$_{IN115}$-C_L-GIVEQC[3]C[4]X$_{IN127}$SIC[5]SLYQLENYC[6]X$_{IN128}$X$_{IN129}$-L_j-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE,或者,

[0709] U_L-X_{IN107}HLC[1]GSHLVEALYLVC[2]GERGFX$_{IN110}$X$_{IN111}$X$_{IN112}$X$_{IN113}$X$_{IN114}$X$_{IN115}$-C_L-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N-(GGGGS)$_m$-X_L-(GGGGS)$_n$-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE,或者,

[0710] U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKT-C_L-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N-(GGGGS)$_m$-X_L-(GGGGS)$_n$-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE,或者,

[0711] U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKT-C_L-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N-(GGGGS)$_n$-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者,

[0712] U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE-L_j-X_{IN107}HLC[1]GSX$_{IN108}$LVEALYLVC[2]GEX$_{IN109}$GFX$_{IN110}$X$_{IN111}$X$_{IN112}$X$_{IN113}$X$_{IN114}$X$_{IN115}$-C_L-GIVEQC[3]C[4]X$_{IN127}$SIC[5]SLYQLENYC[6]X$_{IN128}$X$_{IN129}$;或者,

[0713] U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_m$-X_L-(GGGGS)$_n$-X_{IN107}HLC[1]GSHLVEALYLVC[2]GERGFX$_{IN110}$X$_{IN111}$X$_{IN112}$X$_{IN113}$X$_{IN114}$X$_{IN115}$-C_L-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]X$_{IN128}$X$_{IN129}$,或者,

[0714] U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_m$-X_L-(GGGGS)$_n$-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKT-C_L-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;或者,

[0715] U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_n$-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKT-C_L-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;或者,

[0716] U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$T

AMEADQPVSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_m$-X_L-(GGGGS)$_n$-FVNQHLCGSHLVEALYLVCGERGFFY TPKTGSGSSSAAAPQTGIVEQCCTSICSLYQLENYCN;

[0717] 上述各序列中,m、n分别是0、1、2、3、4、5或6;其它变量如本文中所定义的;

[0718] [1]-[6]表示半胱氨酸的编号;所述化合物中通过6个半胱氨酸形成3对二硫键,其中A链和B链通过两对链间二硫键连接,A链内存在一对链内二硫键,三对二硫键的具体位置是:$C_{[1]}$和$C_{[4]}$形成二硫键,$C_{[2]}$和$C_{[6]}$形成二硫键,$C_{[3]}$和$C_{[5]}$形成二硫键。

[0719] 胰岛素受体结合多肽-白介素-1受体拮抗蛋白融合蛋白选自:

[0720] IN-1:

[0721] FVNQHLC$_{[1]}$GSHLVEALYLVC$_{[2]}$GERGFFYTPKTGSGSSSAAAPQTGIVEQC$_{[3]}$C$_{[4]}$TSIC$_{[5]}$ SLYQLENYC$_{[6]}$NRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGK MCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEG VMVTKFYFQEDE;(SEQ ID NO:85)

[0722] IN-2:

[0723] FVNQHLC$_{[1]}$GSHLVEALYLVC$_{[2]}$GERGFFYTPKTGSGSSSAAAPQTGIVEQC$_{[3]}$C$_{[4]}$TSIC$_{[5]}$ SLYQLENYC$_{[6]}$NRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGK MCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEG VMVTKFYFQEDE;(SEQ ID NO:86)

[0724] IN-3:

[0725] FVNQHLC$_{[1]}$GSHLVEALYLVC$_{[2]}$GERGFFYTPKTGSGSSSAAAPQTGIVEQC$_{[3]}$C$_{[4]}$TSIC$_{[5]}$ SLYQLENYC$_{[6]}$NRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGK MSLSSVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLSTAMEADQPVSLTNMPDEG VMVTKFYFQEDE;(SEQ ID NO:87)

[0726] IN-4:

[0727] FVNQHLC$_{[1]}$GSHLVEALYLVC$_{[2]}$GERGFFYTPKTGSGSSSAAAPQTGIVEQC$_{[3]}$C$_{[4]}$TSIC$_{[5]}$ SLYQLENYC$_{[6]}$NGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLG IHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTN MPDEGVMVTKFYFQEDE;(SEQ ID NO:88)

[0728] IN-5:

[0729] FVNQHLC$_{[1]}$GSHLVEALYLVC$_{[2]}$GERGFFYTPKTGSGSSSAAAPQTGIVEQC$_{[3]}$C$_{[4]}$TSIC$_{[5]}$ SLYQLENYC$_{[6]}$NGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLG IHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTN MPDEGVMVTKFYFQEDE;(SEQ ID NO:89)

[0730] IN-6:

[0731] FVNQHLC$_{[1]}$GSHLVEALYLVC$_{[2]}$GERGFFYTPKTGSGSSSAAAPQTGIVEQC$_{[3]}$C$_{[4]}$TSIC$_{[5]}$ SLYQLENYC$_{[6]}$NGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLG IHGGKMSLSSVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLSTAMEADQPVSLTN MPDEGVMVTKFYFQEDE;(SEQ ID NO:90)

[0732] IN-7:

[0733] FVNQHLC$_{[1]}$GSHLVEALYLVC$_{[2]}$GERGFFYTPKTGSGSSSAAAPQTGIVEQC$_{[3]}$C$_{[4]}$TSIC$_{[5]}$

SLYQLENYC[6]NGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPH ALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQP VSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:91)

[0734] IN-8：

[0735] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5] SLYQLENYC[6]NGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPH ALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQP VSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:92)

[0736] IN-9：

[0737] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5] SLYQLENYC[6]NGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPH ALFLGIHGGKMSLSSVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLSTAMEADQP VSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:93)

[0738] IN-10：

[0739] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5] SLYQLENYC[6]NGGGGSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVV PIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAM EADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:94)

[0740] IN-11：

[0741] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5] SLYQLENYC[6]NGGGGSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVV PIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAM EADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:95)

[0742] IN-12：

[0743] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5] SLYQLENYC[6]NGGGGSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVV PIEPHALFLGIHGGKMSLSSVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLSTAM EADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:96)

[0744] IN-13：

[0745] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6] NRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDE TRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQE DE;(SEQ ID NO:97)

[0746] IN-14：

[0747] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6] NRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDE TRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQE DE;(SEQ ID NO:98)

[0748] IN-15：

[0749] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMSLSSVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLSTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:99)

[0750] IN-16：

[0751] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:100)

[0752] IN-17：

[0753] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:101)

[0754] IN-18：

[0755] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMSLSSVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLSTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:102)

[0756] IN-19：

[0757] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:103)

[0758] IN-20：

[0759] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:104)

[0760] IN-21：

[0761] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMSLSSVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLSTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:105)

[0762] IN-22：

[0763] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NGGGGSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:106)

[0764] IN-23：

[0765] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NGGGGSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；(SEQ ID NO:107)

[0766] IN-24：

[0767] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NGGGGSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMSLSSVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLSTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；(SEQ ID NO:108)

[0768] IN-25：

[0769] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC[S-马来酰亚胺-$(CH_2)_4$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:109)

[0770] IN-26：

[0771] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC[S-CH_2-CONH-$(CH_2CH_2O)_2$-$(CH_2)_2$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)]ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:110)

[0772] IN-27：

[0773] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-CH_2-CONH-PEG20K)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:111)

[0774] IN-28：

[0775] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-$(CH_2)_{15}$-COOH)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)；(SEQ ID NO:112)

[0776] IN-62

[0777] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDEGGGGSGGGGSFVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N；(SEQ ID NO:146)

[0778] IN-63

[0779] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDEGGGGSGGGGSFVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;(SEQ ID NO:147)

[0780] IN-64:

[0781] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMSLSSVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLSTAMEADQPVSLTNMPDEGVMVTKFYFQEDEGGGGSGGGGSFVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;(SEQ ID NO:148)

[0782] IN-65

[0783] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVCITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDEGGGGSGGGGSFVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;(SEQ ID NO:149)

[0784] IN-66

[0785] MRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDEGGGGSCGGGGSGGGGSFVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;(SEQ ID NO:150)

[0786] IN-67

[0787] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NGGGGSGGGGSCGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:151)

[0788] 本部分序列中,[1]-[6]表示半胱氨酸的编号;所述化合物中通过6个半胱氨酸形成3对二硫键,其中A链和B链通过两对链间二硫键连接,A链内存在一对链内二硫键,三对二硫键的具体位置是:C[1]和C[4]形成二硫键,C[2]和C[6]形成二硫键,C[3]和C[5]形成二硫键。

[0789] 在一个实施方式中,胰岛素受体结合多肽与白介素-1受体拮抗蛋白与生物大分子形成单链化合物,所述融合蛋白的结构为(从左到右对应氨基酸序列从N末端到C末端):

[0790] 胰岛素受体结合多肽-连接基(或间隔基)-生物大分子-连接基(或间隔基)-白介素-1受体拮抗蛋白;

[0791] 胰岛素受体结合多肽-连接基(或间隔基)-白介素-1受体拮抗蛋白-连接基(或间隔基)-生物大分子;

[0792] 生物大分子-连接基(或间隔基)-胰岛素受体结合多肽-连接基(或间隔基)-白介素-1受体拮抗蛋白;

[0793] 生物大分子-连接基(或间隔基)白介素-1受体拮抗蛋白-连接基(或间隔基)-胰岛素受体结合多肽;

[0794] 白介素-1受体拮抗蛋白-连接基(或间隔基)-生物大分子-连接基(或间隔基)-胰岛素受体结合多肽;或者

[0795] 白介素-1受体拮抗蛋白-连接基(或间隔基)-胰岛素受体结合多肽-连接基(或间隔基)-生物大分子；

[0796] 其中生物大分子可以是白蛋白或IgG Fc等。

[0797] 在一个实施方式中,包含人白蛋白的融合蛋白序列为：

[0798] DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHT
LFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIAR
RHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLS
QRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVEND
EMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAK
VFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPC
AEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIK
KQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL-(GGGGS)$_m$-
FVNQHLC$_{[1]}$GSHLVEALYLVC$_{[2]}$GERGFFYTPKT-C$_L$-GIVEQC$_{[3]}$C$_{[4]}$TSIC$_{[5]}$SLYQLENYC$_{[6]}$N-(GGGGS)$_n$-
RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VK
SGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEG
VMVTKFYFQEDE;或

[0799] DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHT
LFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIAR
RHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLS
QRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVEND
EMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAK
VFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPC
AEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIK
KQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL-(GGGGS)$_m$-RPSGR
KSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDET
RLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTK
FYFQEDE-(GGGGS)$_n$-FVNQHLC$_{[1]}$GSHLVEALYLVC$_{[2]}$GERGFFYTPKT-C$_L$-GIVEQC$_{[3]}$C$_{[4]}$TSIC$_{[5]}$
SLYQLENYC$_{[6]}$N;或者，

[0800] FVNQHLC$_{[1]}$GSHLVEALYLVC$_{[2]}$GERGFFYTPKT-C$_L$-GIVEQC$_{[3]}$C$_{[4]}$TSIC$_{[5]}$SLYQLENYC$_{[6]}$N-
(GGGGS)$_m$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLH
TLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIA
RRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARL
SQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVEN
DEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYA
KVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMP
CAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQI
KKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL-(GGGGS)$_n$-RPSG
RKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDE
TRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVT

KFYFQEDE;或者，

[0801] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKT-C_L-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N-(GGGGS)$_m$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_n$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL;或者，

[0802] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDEGGGGSGGGGSDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL;或者，

[0803] X$_{IL0}$RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_m$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL-(GGGGS)$_n$-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKT-C_L-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;或者，

[0804] X$_{IL0}$RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEAD

QPVSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_m$-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKT-C_L-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N-(GGGGS)$_n$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL;

[0805] 其中,上述各融合蛋白中,m、n是0、1、2、3、4、5或6,其它各变量如本文中所定义的。

[0806] IN-68:

[0807] DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGLGGGGSGGGGSFVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:152)

[0808] IN-69:

[0809] DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGLGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDEGGGGSGGGGSFVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;(SEQ ID NO:153)

[0810] IN-70:

[0811] MRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCL

SCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMV TKFYFQEDEGGGGSGGGGSDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADE SAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEET FLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGER AFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLE KSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCC AAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKC CKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADI CTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGLGGGG SGGGGSFVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPKTGAGSSSAAAPQTGIVEQC[3]C[4]TSIC[5] SLYQLENYC[6]N(SEQ ID NO:154)。

[0812] (2)白介素-1受体拮抗蛋白-连接基或间隔基-胰岛素受体结合多肽二聚蛋白/交联蛋白

[0813] 如果胰岛素受体结合多肽通过化学反应与连接基相连,再与白介素-1受体拮抗蛋白连接,胰岛素受体结合多肽上的反应官能团和反应位点有一定的选择规律。

[0814] 天然人胰岛素只有B29这1个赖氨酸。单链胰岛素受体结合多肽通过N末端的α-氨基、链内或末端的赖氨酸侧链的ε-氨基或半胱氨酸侧链的巯基与连接基相连。双链胰岛素受体结合多肽通过B链N末端的α-氨基、B链N末端或C末端的赖氨酸侧链的ε-氨基或半胱氨酸侧链的巯基或者A链C末端的赖氨酸侧链的氨基或半胱氨酸侧链的巯基与连接基相连。

[0815] 在一个实施方式中,融合蛋白的序列为:

[0816] U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHG GKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(连接基-胰岛素受体结合多肽)PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者,

[0817] U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHG GKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVC(连接基-胰岛素受体结合多肽)ITDLSENRKQDKRFAFIRSDSG PTTSFESAASPGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者,

[0818] (胰岛素受体结合多肽-连接基)-C_{IL0}-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAG YLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFI RSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE,或者

[0819] U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHG GKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$T AMEADQPVSLTNMPDEGVMVTKFYFQEDEC$_{IL153}$(连接基-胰岛素受体结合多肽),

[0820] 各融合蛋白中,各变量如本文中所定义的。

[0821] 在一个实施方式中,连接基的一端是N-羟基琥珀酰亚胺(NHS酯),与胰岛素受体结合多肽的赖氨酸侧链氨基反应,另一端是马来酰亚胺或碘代乙酰胺活化的修饰基团,与白介素-1受体拮抗蛋白0、6、8、9、84、116、141或153位的半胱氨酸反应形成共价键连接;在一个实施方式中,连接基的一端是马来酰亚胺或碘代乙酰胺活化的修饰基团,与白介素-1受体拮抗蛋白0、6、8、9、84、116、141或153位的半胱氨酸反应形成共价键连接。另一端是醛基,与胰岛素受体结合多肽的N末端氨基反应,通过还原性胺化形成共价键。在一个实施方式

中，连接基的一端是NHS酯，与胰岛素受体结合多肽的赖氨酸侧链氨基反应，另一端是醛基，与白介素-1受体结合多肽的N末端氨基反应，通过还原性胺化形成共价键。

[0822] 胰岛素受体结合多肽是本发明所述单链或双链结构。在一种实施方式中，胰岛素受体结合多肽是天然人胰岛素、天然人胰岛素desB30T、赖脯胰岛素、门冬胰岛素、赖谷胰岛素等。B链N末端的α-氨基或链内赖氨酸侧链的ε氨基可以与连接基一端的NHS酯反应。在一种实施方式中，胰岛素受体结合多肽是经过修饰的缀合物，例如甘精胰岛素、地特胰岛素等。

[0823] 单链胰岛素受体结合多肽可以是以下序列之一：

[0824] U_L-X_{IN107}HLC[1]GSX_{IN108}LVEALYLVC[2]GEX_{IN109}GF$X_{IN110}$$X_{IN111}$$X_{IN112}$$X_{IN113}$$X_{IN114}$$X_{IN115}$-$C_L$-GIVEQC[3]C[4]$X_{IN127}$SICSLYQLENYC[6]$X_{IN128}$$X_{IN129}$；或者，

[0825] U_L-X_{IN107}HLC[1]GSHLVEALYLVC[2]GERGF$X_{IN110}$$X_{IN111}$$X_{IN112}$$X_{IN113}$$X_{IN114}$$X_{IN115}$-$C_L$-GIVEQC[3]C[4]TSICSLYQLENYC[6]$X_{IN128}$$X_{IN129}$；或者，

[0826] U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$T-C_L-GIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N；或者，

[0827] U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$TGKGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N；或者，

[0828] U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$TGSGKSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N；或者，

[0829] U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$TGSGSKSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N；或者

[0830] U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$TGSGSSKAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N；或者，

[0831] U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$TGSGSSSKAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N；或者，

[0832] U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$TGSGSSSAKAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N；或者，

[0833] U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$TGSGSSSAAKPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N；或者，

[0834] U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$TGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NK；或者，

[0835] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPX$_{IN114}$TGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N；或者，

[0836] U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAKPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N；或者，

[0837] U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAKAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N；或者，

[0838] U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSKAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N；或者，

[0839] U_L-FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]

SLYQLENYC[6]NK;或者，

[0840] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N;

[0841] 各多肽中的变量如本文中所定义的;

[0842] 单链胰岛素受体结合多肽通过N末端的α-氨基或赖氨酸侧链的ε-氨基与连接基相连。

[0843] 用于形成二聚蛋白/交联蛋白的白介素-1受体拮抗蛋白可以是：

[0844] U_L-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者，

[0845] U_L-CRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者，

[0846] U_L-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDEC;

[0847] 各蛋白中的各变量如本文中所定义的。

[0848] 胰岛素受体结合多肽-连接基或间隔基-白介素-1受体拮抗蛋白可以是：

[0849] (胰岛素受体结合多肽-连接基)RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者

[0850] (胰岛素受体结合多肽-连接基)CRPSGRKSSKMQAFRIWDVNQKTF YLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE;各蛋白中的各变量如本文中所定义的。

[0851] 胰岛素受体结合多肽与白介素-1受体拮抗蛋白的二聚蛋白/交联蛋白的序列选自：

[0852] IN-29：

[0853] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPRTGK(N^{ε}-PEG12-马来酰亚胺-IL-1ra)GSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQ LENYC[6]N(SEQ ID NO:113),其中IL-1ra的序列为：

[0854] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(SEQ ID NO:194)，

[0855] 连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与胰岛素受体结合多肽赖氨酸侧链的氨基反应,马来酰亚胺与IL-1ra带下划线的116位的半胱氨酸侧链巯基反应。

[0856] IN-30：

[0857] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPRTGK(N^{ε}-PEG12-马来酰亚胺-白介素-1受体拮抗蛋白)GSSSAAAPQT GIVEQC[3]C[4]TSIC[5]SLYQ LENYC[6]N;(SEQ ID NO:114)

[0858] 其中白介素-1受体拮抗蛋白的序列如下：

[0859] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLS CVKSGDETRLQLEAVCITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVT KFYFQEDE(SEQ ID NO:195)，

[0860] 连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与胰岛素受体结合多肽赖氨酸侧链的氨基反应，马来酰亚胺与白介素-1受体拮抗蛋白带下划线的84位半胱氨酸侧链巯基反应。

[0861] IN-31：

[0862] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPRTGK(N$^{\varepsilon}$-PEG20K-马来酰亚胺-IL-1ra) GSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQ LENYC[6]N，(SEQ ID NO:115)，其中IL-1ra的序列为SEQ ID NO:194，连接基马来酰亚胺-PEG20K-NHS的N-羟基琥珀酰亚胺与胰岛素受体结合多肽赖氨酸侧链的氨基反应，马来酰亚胺与IL-1ra带下划线的116位的半胱氨酸侧链巯基反应。

[0863] IN-32：

[0864] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPRTGK(N$^{\varepsilon}$-PEG20K-马来酰亚胺-白介素-1受体拮抗蛋白)GSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N，(SEQ ID NO:116)，其中白介素-1受体拮抗蛋白的序列为SEQ ID NO:195，连接基马来酰亚胺-PEG20K-NHS的N-羟基琥珀酰亚胺与胰岛素受体结合多肽赖氨酸侧链的氨基反应，马来酰亚胺与白介素-1受体拮抗蛋白带下划线的84位半胱氨酸侧链巯基反应。

[0865] IN-33：

[0866] F[N$^{\alpha}$-(N$^{\alpha}$-(HOOC(CH$_2$)$_{14}$CO)-γ-L-Glu)]VNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPRTGK (N$^{\varepsilon}$-PEG12-马来酰亚胺-IL-1ra)GSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQ LENYC[6]N(SEQ ID NO:117)；其中IL-1ra的序列为SEQ ID NO:194，连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与胰岛素受体结合多肽赖氨酸侧链的氨基反应，马来酰亚胺与IL-1ra带下划线的116位的半胱氨酸侧链巯基反应。

[0867] IN-34：

[0868] F[N$^{\alpha}$-(N$^{\alpha}$-(HOOC(CH$_2$)$_{16}$CO)-γ-L-Glu)]VNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPRTGK (N$^{\varepsilon}$-PEG12-马来酰亚胺-白介素-1受体拮抗蛋白)GSSSAAAPQTGIVEQC[3]C[4]TSIC[5] SLYQLENYC[6]N，(SEQ ID NO:118)，其中白介素-1受体拮抗蛋白的序列为SEQ ID NO:195，连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与胰岛素受体结合多肽赖氨酸侧链的氨基反应，马来酰亚胺与白介素-1受体拮抗蛋白带下划线的84位半胱氨酸侧链巯基反应。

[0869] IN-35：

[0870] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLS CVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG12-人胰岛素) PGWFLCTAMEAD QPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO: 119)；

[0871] 连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与人胰岛素B链N末端的α-氨基反应，马来酰亚胺与IL-1ra 116位的半胱氨酸侧链巯基反应。

[0872] IN-36：

[0873] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLS

CVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG12-胰岛素受体结合多肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:120)，

[0874] 连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与胰岛素受体结合多肽$N^{\varepsilon B29}$-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)des(B30)人胰岛素B链N末端的α-氨基反应，马来酰亚胺与IL-1ra 116位的半胱氨酸侧链巯基反应。

[0875] IN-37：

[0876] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG20K-人胰岛素)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:121)；

[0877] 连接基马来酰亚胺-PEG20K-NHS的N-羟基琥珀酰亚胺与人胰岛素B链N末端的α-氨基反应，马来酰亚胺与IL-1ra 116位的半胱氨酸侧链巯基反应。

[0878] IN-38：

[0879] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-PEG 12-人胰岛素)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTA MEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:122)；

[0880] 其中，连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与人胰岛素B链N末端的α-氨基反应，马来酰亚胺与白介素-1受体拮抗蛋白84位半胱氨酸侧链巯基反应。

[0881] IN-39：

[0882] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-PEG 20K-人胰岛素)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:123)；

[0883] 其中，连接基马来酰亚胺-PEG20K-NHS的N-羟基琥珀酰亚胺与人胰岛素B链N末端的α-氨基反应，马来酰亚胺与白介素-1受体拮抗蛋白84位半胱氨酸侧链巯基反应。

[0884] IN-40：

[0885] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-PEG12-胰岛素受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWF LCTAMEAD QPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:124)；

[0886] 其中，连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与胰岛素受体结合多肽$N^{\varepsilon B29}$-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu)des(B30)人胰岛素的B链N末端的α-氨基反应，马来酰亚胺与白介素-1受体拮抗蛋白84位的半胱氨酸侧链巯基反应。

[0887] IN-41：

[0888] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG12-人胰岛素desB30T)PGWFLCTAMEADQPVSLTNMPDEGV MVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID

NO:125)；

[0889] 其中，连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与人胰岛素desB30T B29赖氨酸的ε-氨基反应，马来酰亚胺与IL-1ra 116位的半胱氨酸侧链巯基反应。

[0890] IN-42：

[0891] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLS CVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG20K-人胰岛素desB30T)

[0892] PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:126)；

[0893] 其中，连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与人胰岛素desB30T B29赖氨酸的ε-氨基反应，马来酰亚胺与IL-1ra 116位的半胱氨酸侧链巯基反应。

[0894] IN-43：

[0895] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLS CVKSGDETRLQLEAVC(S-马来酰亚胺-PEG 12-人胰岛素desB30T)ITDLSENRKQDKRFAFIRSDSGP TTSFESAASPG WFLCTA MEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:127)，

[0896] 其中，连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与人胰岛素desB30T B29赖氨酸的ε-氨基反应，马来酰亚胺与白介素-1受体拮抗蛋白84位半胱氨酸侧链巯基反应。

[0897] IN-44：

[0898] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLS CVKSGDETRLQLEAVC(S-马来酰亚胺-PEG 20K-人胰岛素desB30T)ITDLSENRKQDKRFAFIRSDSG PTTSFESAASPG WFLCTA MEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:128)，

[0899] 其中，连接基马来酰亚胺-PEG20K-NHS的N-羟基琥珀酰亚胺与人胰岛素desB30T B29赖氨酸的ε-氨基反应，马来酰亚胺与白介素-1受体拮抗蛋白84位半胱氨酸侧链巯基反应。

[0900] IN-45：

[0901] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPRTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5] SLYQLENYC[6]NK(N^{ε}-PEG12-马来酰亚胺-IL-1ra)(SEQ ID NO:129)，其中，IL-1ra的序列是SEQ ID NO:194；

[0902] 其中，连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与单链胰岛素C末端赖氨酸侧链ε-氨基反应，马来酰亚胺与IL-1ra带下划线的116位的半胱氨酸侧链巯基反应。

[0903] IN-46：

[0904] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPRTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5] SLYQLENYC[6]NK(N^{ε}-PEG20K-马来酰亚胺-IL-1ra)(SEQ ID NO:130)，其中IL-1ra的序列是：SEQ ID NO:194；

[0905] 连接基马来酰亚胺-PEG20K-NHS的N-羟基琥珀酰亚胺与单链胰岛素C末端赖氨酸侧链ε-氨基反应，马来酰亚胺与IL-1ra带下划线的116位的半胱氨酸侧链巯基反应。

[0906] IN-47：

[0907] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPRTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NK(N$^{\varepsilon}$-PEG12-马来酰亚胺-白介素-1受体拮抗蛋白)(SEQ ID NO:131)，白介素-1受体拮抗蛋白的序列是：SEQ ID NO:195；

[0908] 连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与单链胰岛素C末端赖氨酸侧链ε-氨基反应，马来酰亚胺与白介素-1受体拮抗蛋白带下划线的84位半胱氨酸侧链巯基反应。

[0909] IN-48：

[0910] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPRTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]NK(N$^{\varepsilon}$-PEG20K-马来酰亚胺-白介素-1受体拮抗蛋白)(SEQ ID NO:132)，白介素-1受体拮抗蛋白的序列是：SEQ ID NO:195，连接基马来酰亚胺-PEG20K-NHS的N-羟基琥珀酰亚胺与单链胰岛素C末端赖氨酸侧链ε-氨基反应，马来酰亚胺与白介素-1受体拮抗蛋白带下划线的84位半胱氨酸侧链巯基反应。

[0911] IN-49：

[0912] F(N$^{\alpha}$-PEG12-马来酰亚胺-IL-1ra)VNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPRTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N(SEQ ID NO:133)，其中IL-1ra的序列是：

[0913] CRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(SEQ ID NO:196)；

[0914] 连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与单链胰岛素N末端α-氨基反应，马来酰亚胺与白介素-1受体拮抗蛋白N末端的半胱氨酸侧链巯基反应。

[0915] IN-50：

[0916] F(N$^{\alpha}$-PEG20K-马来酰亚胺-IL-1ra)VNQHLC[1]GSHLVEA LYLVC[2]GERGFFYTPRTGSGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N(SEQ ID NO:134)，其中，IL-1ra的序列是：SEQ ID NO:196；

[0917] 连接基马来酰亚胺-PEG20K-NHS的N-羟基琥珀酰亚胺与单链胰岛素N末端α-氨基反应，马来酰亚胺与白介素-1受体拮抗蛋白N末端的半胱氨酸侧链巯基反应。

[0918] IN-51：

[0919] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPRTGK(N$^{\varepsilon}$-PEG12-马来酰亚胺-白介素-1受体拮抗蛋白)GSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N(SEQ ID NO:135)，其中白介素-1受体拮抗蛋白的序列是：SEQ ID NO:196；

[0920] 连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与单链胰岛素赖氨酸侧链ε-氨基反应，马来酰亚胺与白介素-1受体拮抗蛋白N末端的半胱氨酸侧链巯基反应。

[0921] IN-52：

[0922] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPRTGK(N$^{\varepsilon}$-PEG20K-马来酰亚胺-白介素-1受体拮抗蛋白)GSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLEN YC[6]N(SEQ ID NO:136)；

[0923] 其中，白介素-1受体拮抗蛋白的序列是：SEQ ID NO:196；

[0924] 其中，连接基马来酰亚胺-PEG20K-NHS的N-羟基琥珀酰亚胺与单链胰岛素赖氨酸

侧链ε-氨基反应，马来酰亚胺与白介素-1受体拮抗蛋白N末端的半胱氨酸侧链巯基反应。

[0925] IN-53：

[0926] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPRTGSGSSSAK(N^{ε}-PEG12-马来酰亚胺-白介素-1受体拮抗蛋白)APQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N(SEQ ID NO:137)，其中白介素-1受体拮抗蛋白的序列是：SEQ ID NO:196；

[0927] 其中，连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与单链胰岛素赖氨酸侧链ε-氨基反应，马来酰亚胺与白介素-1受体拮抗蛋白N末端的半胱氨酸侧链巯基反应。

[0928] IN-54：

[0929] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPRTGSGSSSAK(N^{ε}-PEG20K-马来酰亚胺-白介素-1受体拮抗蛋白)APQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N(SEQ ID NO:138)，其中白介素-1受体拮抗蛋白的序列是：SEQ ID NO:196；

[0930] 其中，连接基马来酰亚胺-PEG20K-NHS的N-羟基琥珀酰亚胺与单链胰岛素赖氨酸侧链ε-氨基反应，马来酰亚胺与白介素-1受体拮抗蛋白N末端的半胱氨酸侧链巯基反应。

[0931] IN-55：

[0932] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAK(N^{ε}-PEG12-马来酰亚胺-IL-1ra)APQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N(SEQ ID NO:139)，其中IL-1ra的序列为SEQID NO:194，

[0933] 连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与胰岛素受体结合多肽赖氨酸侧链的氨基反应，马来酰亚胺与IL-1ra带下划线的116位的半胱氨酸侧链巯基反应。

[0934] IN-56：

[0935] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFGSGSSSAK(N^{ε}-PEG12-马来酰亚胺-白介素-1受体拮抗蛋白)APQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N(SEQ ID NO:140)，其中白介素-1受体拮抗蛋白的序列为：SEQ ID NO:195，连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与胰岛素受体结合多肽赖氨酸侧链的氨基反应，马来酰亚胺与白介素-1受体拮抗蛋白带下划线的84位半胱氨酸侧链巯基反应。

[0936] IN-57：

[0937] C(S-马来酰亚胺-PEG12-人胰岛素)RPSGRKSSKMQAFRIWD VNQKTFYL RNNQLVAGYLQ GPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFE SAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:141)，

[0938] 连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与人胰岛素B链N末端α-氨基反应，马来酰亚胺与白介素-1受体拮抗蛋白N末端的半胱氨酸侧链巯基反应。

[0939] IN-58：

[0940] C(S-马来酰亚胺-PEG12-胰岛素受体结合多肽)RPSGRKSSKMQAFRIWD VNQKTFYLRN NQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRS DSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:142)，

[0941] 连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与胰岛素受体结合多肽$N^{\varepsilon B29}$-(N^{α}-(HOOC(CH_2)$_{14}$CO)-γ-Glu)des(B30)人胰岛素的B链N末端的α-氨基反应，马来酰亚胺与

白介素-1受体拮抗多肽N末端的半胱氨酸侧链巯基反应。

[0942] IN-59：

[0943] C(S-马来酰亚胺-PEG12-人胰岛素desB30T)RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:143)，

[0944] 连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与人胰岛素desB30T B29赖氨酸侧链ε-氨基反应，马来酰亚胺与白介素-1受体拮抗多肽N末端的半胱氨酸侧链巯基反应。

[0945] IN-60：

[0946] MRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDEC(S-马来酰亚胺-PEG12-人胰岛素)(S是半胱氨酸侧链的硫原子)(SEQ ID NO:144)，

[0947] 连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与人胰岛素B链N末端α-氨基反应，马来酰亚胺与白介素-1受体拮抗蛋白C末端的半胱氨酸侧链巯基反应。

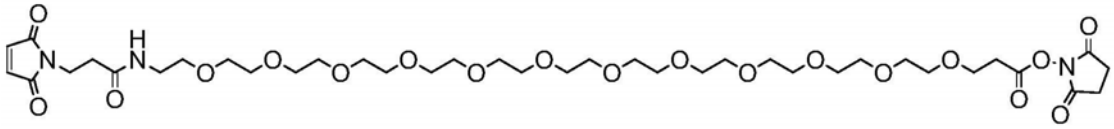
[0948] IN-61：

[0949] MRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDEC(S-马来酰亚胺-PEG12-人胰岛素desB30T)(S是半胱氨酸侧链的硫原子)(SEQ ID NO:145)，

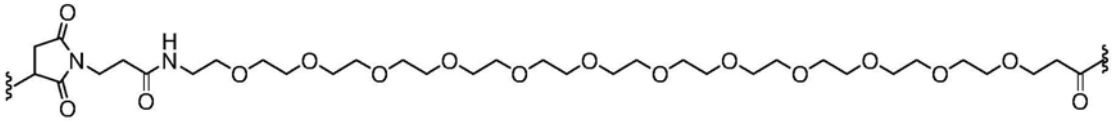
[0950] 连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与人胰岛素desB30T B29赖氨酸侧链ε-氨基反应，马来酰亚胺与白介素-1受体拮抗多肽C末端的半胱氨酸侧链巯基反应。

[0951] 在本部分序列中，[1]-[6]表示半胱氨酸的编号；所述化合物中通过6个半胱氨酸形成3对二硫键，其中A链和B链通过两对链间二硫键连接，A链内存在一对链内二硫键，三对二硫键的具体位置是：$C_{[1]}$和$C_{[4]}$形成二硫键，$C_{[2]}$和$C_{[6]}$形成二硫键，$C_{[3]}$和$C_{[5]}$形成二硫键。

[0952] 马来酰亚胺-PEG12-NHS试剂的结构如下所示：

[0953] 

[0954] 该试剂与白介素-1受体拮抗蛋白和胰岛素受体结合多肽反应后的结构如下所示：

[0955] 

[0956] 3、GIP受体结合多肽和白介素-1受体拮抗蛋白的融合蛋白

[0957] 在一个实施方式中，GIP受体结合多肽的序列：

[0958] $(X_{GI1}X_{GI2}X_{GI3}GT)_{t0}X_{GI6}X_{GI7}SDX_{GI10}SX_{GI12}X_{GI13}X_{GI14}DX_{GI16}X_{GI17}X_{GI18}QX_{GI20}X_{GI21}FX_{GI23}X_{GI24}WLX_{GI27}X_{GI28}X_{GI29}X_{GI30}X_{GI31}X_{GI32}X_{GI33}X_{GI34}X_{GI35}X_{GI36}X_{GI37}X_{GI38}X_{GI39}X_{GI40}X_{GI41}X_{GI42}X_{GI43}$，其中，

[0959] X_{GI1}是酪氨酸、N-乙酰基酪氨酸、焦谷氨酰-酪氨酸、葡萄糖醇-酪氨酸、D-组氨酸、α,α-2甲基咪唑乙酸(DMIA)、N-甲基组氨酸、α-甲基组氨酸、咪唑乙酸、脱氨组氨酸、羟基组

氨酸、乙酰组氨酸、高组氨酸、N-棕榈酸-酪氨酸、N-Fmoc-酪氨酸或缺失；X_{GI2}是丙氨酸、D-丙氨酸、D-丝氨酸、丝氨酸、缬氨酸、甘氨酸、N-甲基丝氨酸、N-甲基丙氨酸、2-甲基丙氨酸或缺失；X_{GI3}是谷氨酸、羟基脯氨酸、脯氨酸或缺失；X_{GI6}是苯丙氨酸或缺失；X_{GI7}是异亮氨酸或苏氨酸；X_{GI10}是酪氨酸、色氨酸、苯丙氨酸、缬氨酸、赖氨酸、鸟氨酸、谷氨酸、亮氨酸、通式1或通式2；X_{GI12}是异亮氨酸、丝氨酸、赖氨酸、精氨酸、通式1或通式2；X_{GI13}是丙氨酸、谷氨酰胺或酪氨酸；X_{GI14}是甲硫氨酸或亮氨酸；X_{GI16}是赖氨酸、精氨酸、丝氨酸、谷氨酸、谷氨酰胺、高谷氨酸、高半胱氨酸、苏氨酸、甘氨酸、2-甲基丙氨酸、通式1或通式2；X_{GI17}是异亮氨酸、谷氨酰胺、谷氨酸、精氨酸、通式1或通式2；X_{GI18}是组氨酸、丙氨酸、精氨酸、丝氨酸、苏氨酸或甘氨酸；X_{GI20}是谷氨酰胺、赖氨酸、丙氨酸、丝氨酸、苏氨酸、瓜氨酸、精氨酸、鸟氨酸、2-甲基丙氨酸、其它α,α-双取代氨基酸、通式1或通式2；X_{GI21}是天冬氨酸、谷氨酸、高谷氨酸、高半胱氨酸、亮氨酸、通式1或通式2；X_{GI23}是缬氨酸或异亮氨酸；X_{GI24}是谷氨酰胺、谷氨酸、天冬酰胺、丙氨酸、丝氨酸、苏氨酸、2-甲基丙氨酸、通式1或通式2；X_{GI27}是亮氨酸、异亮氨酸、正亮氨酸、赖氨酸、缬氨酸、甲硫氨酸、通式1或通式2；X_{GI28}是甘氨酸、丙氨酸、赖氨酸、天冬酰胺、通式1或通式2；X_{GI29}是谷氨酰胺、甘氨酸、苏氨酸、丙氨酸、通式1或通式2；X_{GI30}是赖氨酸、精氨酸、甘氨酸、通式1或通式2；X_{GI31}是-NH_2、甘氨酸、脯氨酸或缺失；X_{GI32}是赖氨酸、精氨酸、丝氨酸、通式1、通式2或缺失；X_{GI33}是赖氨酸、精氨酸、丝氨酸、通式1、通式2或缺失；X_{GI34}是天冬酰胺、甘氨酸或缺失；X_{GI35}是天冬酰胺、丙氨酸或缺失；X_{GI36}是色氨酸、脯氨酸或缺失；X_{GI37}是赖氨酸、精氨酸、脯氨酸、通式1、通式2或缺失；X_{GI38}是组氨酸、脯氨酸或缺失；X_{GI39}是天冬酰胺、丝氨酸或缺失；X_{GI40}是异亮氨酸、-NH_2、通式1、通式2或缺失；X_{GI41}是苏氨酸或缺失；X_{GI42}是谷氨酰胺或缺失；X_{GI43}是赖氨酸、半胱氨酸、PSSGAPPPS、通式3、通式4或缺失；t0是0或1。

[0960] 在一个实施方式中，GIP第31-42位的序列可以从C末端起有1-12个氨基酸的删减。在一个实施方式中，GIP第31-42位的序列可以替换为PSSGAPPPS、GPSSGAPPPS、X_{GI}PSSGAPPPS、PSSGAPPPX_{GI}-NH_2、PSSGAPPPSX_{GI}-NH_2，其中X_{GI}是通式1或通式2。

[0961] GIP受体结合多肽和白介素-1受体拮抗蛋白能够通过相似或不同的机理保护胰岛β细胞，治疗糖尿病。因此，将两种化合物连接后形成的融合蛋白、二聚蛋白或交接蛋白可以通过两种化合物的协同作用，达到比单独使用其中一种化合物更优异的治疗效果。另外，GIP受体的一个主要分布组织就是胰岛。GIP受体结合多肽可以为融合蛋白、二聚蛋白或交接蛋白起到靶向作用，使白介素-1受体拮抗蛋白富集于胰岛及胰岛周围，更有效地发挥消炎等作用。

[0962] GIP受体结合多肽与白介素-1受体拮抗蛋白通过可选的连接基(或间隔基)相连，可以有多种不同的连接方式。

[0963] (1)GIP受体结合多肽-连接基或间隔基-白介素-1受体拮抗蛋白

[0964] 在一个实施方式中，GIP受体结合多肽与白介素-1受体拮抗蛋白通过连接基形成单链化合物，所述融合蛋白的结构为(从左到右对应氨基酸序列从N末端到C末端)：

[0965] GIP受体结合多肽-连接基(或间隔基)-白介素-1受体拮抗蛋白；或者

[0966] 白介素-1受体拮抗蛋白-连接基(或间隔基)-GIP-1受体结合多肽。

[0967] 在一种实施方式中，所述融合蛋白的序列是：

[0968] U_L-($X_{GI1}X_{GI2}X_{GI3}$GT)$_{t0}X_{GI6}X_{GI7}$SDX_{GI10}S$X_{GI12}X_{GI13}X_{GI14}$D$X_{GI16}X_{GI17}X_{GI18}$Q$X_{GI20}X_{GI21}$F$X_{GI23}X_{GI24}$WL$X_{GI27}X_{GI28}X_{GI29}X_{GI30}X_{GI31}X_{GI32}X_{GI33}X_{GI34}X_{GI35}X_{GI36}X_{GI37}X_{GI38}X_{GI39}X_{GI40}X_{GI41}X_{GI42}X_{GI43}$-$L_j$-$X_{IL0}$RPSG

RKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMX$_{IL66}$LSX$_{IL69}$VKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLX$_{IL122}$TAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者，

[0969] U_L-(X$_{GI1}$X$_{GI2}$X$_{GI3}$GT)$_{t0}$X$_{GI6}$ISDX$_{GI10}$SX$_{GI12}$AMDX$_{GI16}$IHQQDFVNWLX$_{GI27}$X$_{GI28}$QX$_{GI30}$(GX$_{GI32}$X$_{GI33}$NDWX$_{GI37}$HNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$-(GGGGS)$_m$-X_L-(GGGGS)$_n$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者，

[0970] U_L-X$_{GI1}$X$_{GI2}$X$_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$-(GGGGS)$_m$-X_L-(GGGGS)$_n$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;或者，

[0971] U_L-X$_{GI6}$ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$-(GGGGS)$_m$-X_L-(GGGGS)$_n$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE，

[0972] 上面各序列中，m、n分别是0、1、2、3、4、5或6；t0、t1、t2分别是0或1；其它变量如本文中所定义的。

[0973] 在一个实施方式中，GIP受体结合多肽与白介素-1受体拮抗蛋白与生物大分子形成单链化合物，所述融合蛋白的结构为(从左到右对应氨基酸序列从N末端到C末端)：

[0974] GIP受体结合多肽-连接基(或间隔基)-生物大分子-连接基(或间隔基)-白介素-1受体拮抗蛋白；

[0975] GIP受体结合多肽-连接基(或间隔基)-白介素-1受体拮抗蛋白-连接基(或间隔基)-生物大分子；其中生物大分子可以是白蛋白或IgG Fc等。

[0976] 在一个实施方式中，包含人白蛋白的融合蛋白的序列为：

[0977] (X$_{GI1}$X$_{GI2}$X$_{GI3}$GT)$_{t0}$X$_{GI6}$ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$-(GGGGS)$_m$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL-(GGGGS)$_n$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE，其中，m、n分别是0、1、2、3、4、5或6；其它变量如本文中所定义的。

[0978] 在一个实施方式中，包含人白蛋白的融合蛋白的序列为：

[0979] (X$_{GI1}$X$_{GI2}$X$_{GI3}$GT)$_{t0}$X$_{GI6}$ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$-(GGGGS)$_m$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPH

ALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQP
VSLTNMPDEGVMVTKFYFQEDE-(GGGGS)$_n$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVN
EVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEV
DVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQ
RLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSIS
SKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLR
LAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLV
EVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPK
EFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLV
AASQAALGL,其中,m、n分别是0、1、2、3、4、5或6;其它变量如本文中所定义的。在一个实施方式中,包含人白蛋白的融合蛋白的序列为:

[0980] $(X_{GI1}X_{GI2}X_{GI3}GT)_{t0}X_{GI6}$ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$$(X_{GI1}X_{GI2}X_{GI3}GT)_{t0}X_{GI6}$ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$-(GGGGS)$_m$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCL
SCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMV
TKFYFQEDE-(GGGGS)$_n$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADE
SAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEET
FLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGER
AFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLE
KSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCC
AAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKC
CKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADI
CTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL;

[0981] 在一个实施方式中,包含人白蛋白的融合蛋白的序列为:

[0982] $(X_{GI1}X_{GI2}X_{GI3}GT)_{t0}X_{GI6}$ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$$(X_{GI1}X_{GI2}X_{GI3}GT)_{t0}X_{GI6}$ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$(PSSGAPPPS)$_{t2}$-(GGGGS)$_m$-DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLH
TLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIA
RRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARL
SQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVEN
DEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYA
KVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMP
CAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQI
KKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL-(GGGGS)$_n$-RPSG
RKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQL
EAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;其中,m、n分别是0、1、2、3、4、5或6;其它变量如本文中所定义的。

[0983] 在一个实施方式中,包含IgG1 Fc的融合蛋白的序列为:

[0984] $(X_{GI1}X_{GI2}X_{GI3}GT)_{t0}X_{GI6}$ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$

$(PSSGAPPPS)_{t2}$-$(GGGGS)_m$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE-$(GGGGS)_n$-AEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK，其中，m、n分别是0、1、2、3、4、5或6；其它变量如本文中所定义的。

[0985] 在一个实施方式中，包含IgG1 Fc的融合蛋白的序列为：

[0986] $(X_{GI1}X_{GI2}X_{GI3}GT)_{t0}X_{GI6}$ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$$(PSSGAPPPS)_{t2}$-$(GGGGS)_m$-AEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK-$(GGGGS)_n$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；其中，m、n分别是0、1、2、3、4、5或6；其它变量如本文中所定义的。

[0987] 包含IgG1 Fc的融合蛋白都是二聚蛋白，通过两个单体蛋白的Fc部分的半胱氨酸形成的链间二硫键。

[0988] 在一个实施方式中，IgG4 Fc与白介素-1受体拮抗蛋白的融合蛋白的序列为：$(X_{GI1}X_{GI2}X_{GI3}GT)_{t0}X_{GI6}$ISDYSIAMDKIHQQDFVNWLLAQK(GKKNDWKHNITQ)$_{t1}$$(PSSGAPPPS)_{t2}$-$(GGGGS)_m$-RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAX_{IL116}PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE-$(GGGGS)_n$-AESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTC$_a$VVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC$_a$KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTC$_b$LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSC$_b$SVMHEALHNHYTQKSLSLSLG，其中，m、n分别是0、1、2、3、4、5或6；其它变量如本文中所定义的。

[0989] 所述二聚蛋白是由两个相同的上述序列组成的同型二聚体。每个加下划线的半胱氨酸C与另外一个单体对应位置的半胱氨酸形成链间二硫键；每个单体的C_a之间形成链间二硫键；每个单体的C_b之间形成链间二硫键。

[0990] 在这一部分，GIP受体结合多肽和白介素-1受体拮抗蛋白的融合蛋白选自：

[0991] GI-1:

[0992] YSEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；(SEQ ID NO:155)

[0993] GI-2:

[0994] Ac-YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE；(SEQ ID NO:156)

[0995] GI-3:

[0996] Ac-YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:157)

[0997] GI-4:

[0998] Ac-YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:158)

[0999] GI-5:

[1000] Ac-YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQGGGGSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:159)

[1001] GI-6:

[1002] YAPGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:160)

[1003] GI-7:

[1004] YAPGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:161)

[1005] GI-8:

[1006] YAPGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:162)

[1007] GI-9:

[1008] YAPGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQGGGGSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:163)

[1009] GI-10:

[1010] ISDYSIAMDKIHQQDFVNWLLAQKPSSGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:164)

[1011] GI-11:

[1012] YGEGTFISDYSIAMDKIHQQDFVNWLLAQKPSSGAPPPSGGGGSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:

165)

[1013] GI-12:

[1014] YGEGTFISDYSIAMDKIHQQDFVNWLLAQKPSSGAPPPSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:166)

[1015] GI-13:

[1016] Ac-YAEGTFISDYSIAMDKIHQQDFVNWLLAQKPSSGAPPPSGGGGSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:167)

[1017] GI-14:

[1018] Ac-YAEGTFISDYSIAMDKIHQQDFVNWLLAQKPSSGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:168)

[1019] GI-15:

[1020] Ac-YAEGTFISDYSIAMDKIHQQDFVNWLLAQKPSSGAPPPSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:169)

[1021] GI-16:

[1022] FISDYSIAMDKIHQQDFVNWLLAQKGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:170)

[1023] GI-17:

[1024] FISDYSIAMDKIHQQDFVNWLLAQKGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:171)

[1025] GI-18:

[1026] FISDYSIAMDKIHQQDFVNWLLAQKPSSGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:172)

[1027] GI-19:

[1028] YAPGTFISDYSIAMDKIHQQDFVNWLLAQKRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:173)

[1029] GI-20:

[1030] YAPGTFISDYSIAMDKIHQQDFVNWLLAQKPSSGAPPPSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:174)

[1031] GI-21:

[1032] YAPGTFISDYSIAMDKIHQQDFVNWLLAQKPSSGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;(SEQ ID NO:175)

[1033] GI-22:

[1034] Ac-YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDEGGGGSDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL;(SEQ ID NO:176)

[1035] GI-23:

[1036] YAPGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDEGGGGSDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL;(SEQ ID NO:177)

[1037] (2)白介素-1受体拮抗蛋白-连接基或间隔基-GIP受体结合多肽二聚蛋白/交联蛋白

[1038] 在这类化合物中,连接基(或间隔基)连接到白介素-1受体拮抗蛋白和GIP受体结合多肽非末端的位置。

[1039] 在一个实施方式中,融合蛋白的序列为:

[1040] U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(连接基-GIP受体结合多肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;各变量如本文中所定义的。

[1041] 在另一个实施方式中,融合蛋白的序列为:

[1042] U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(连接基-GIP受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;各变量如本文中所定义的。

[1043] 在一个具体的实施方式中，连接基的分子结构可以是马来酰亚胺-PEG-马来酰亚胺或I-CH_2-CONH-PEG-NHCO-CH_2-I；在一个具体的实施方式中，连接基的分子结构可以是马来酰亚胺-$(CH_2)_n$-马来酰亚胺或I-CH_2-CONH-$(CH_2)_n$-NHCO-CH_2-I，其中n可以是1至30的整数；在一个具体的实施方式中，连接基的分子结构可以是马来酰亚胺-PEG-NHS。GIP受体结合多肽一般可以通过赖氨酸侧链的氨基或半胱氨酸侧链的巯基与连接基反应。

[1044] 在一个实施方式中，GIP受体结合多肽序列可以是：

[1045] U_L-$(X_{GI1}X_{GI2}X_{GI3}GT)_{t0}X_{GI6}ISDX_{GI10}SX_{GI12}AMDX_{GI16}IHQQDFVNWLX_{GI27}X_{GI28}QX_{GI30}(GX_{GI32}X_{GI33}NDWX_{GI37}HNITQ)_{t1}(PSSGAPPPS)_{t2}$，各变量如本文中所定义的。

[1046] 在一个具体的实施方式中，GIP受体结合多肽序列可以为下述序列之一：

[1047] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQC；

[1048] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWCHNITQ；

[1049] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQKGKCNDWKHNITQ；

[1050] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQKGCKNDWKHNITQ；

[1051] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQCGKKNDWKHNITQ；

[1052] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDCIHQQDFVNWLLAQKGKKNDWKHNITQ；

[1053] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSCAMDKIHQQDFVNWLLAQKGKKNDWKHNITQ；

[1054] $X_{GI1}X_{GI2}X_{GI3}$GTFISDCSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQ；

[1055] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQKC；

[1056] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDCIHQQDFVNWLLAQK-NH_2；

[1057] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQKPSSGAPPPSC；

[1058] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQKPSSGAPPPC-NH_2；

[1059] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQCPSSGAPPPS-NH_2；

[1060] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDCIHQQDFVNWLLAQKPSSGAPPPS-NH_2；

[1061] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSCAMDKIHQQDFVNWLLAQKPSSGAPPPS-NH_2；

[1062] $X_{GI1}X_{GI2}X_{GI3}$GTFISDCSIAMDKIHQQDFVNWLLAQKPSSGAPPPS-NH_2；

[1063] FISDYSIAMDKIHQQDFVNWLLAQKC；

[1064] FISDYSIAMDKIHQQDFVNWLLAQC-NH_2；

[1065] FISDYSIAMDCIHQQDFVNWLLAQK-NH_2；

[1066] ISDYSIAMDKIHQQDFVNWLLAQC-NH_2；或者，

[1067] ISDYSIAMDCIHQQDFVNWLLAQK-NH_2；

[1068] 各变量如本文中所定义的；

[1069] GIP-1受体结合多肽通过半胱氨酸侧链的巯基与连接基上的马来酰亚胺或碘代乙酰基反应，连接到白介素-1受体拮抗蛋白。

[1070] 在一个具体的实施方式中，GIP受体结合多肽序列为下述序列之一：

[1071] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDRIHQQDFVNWLLAQRGRRNDWRHNITQK；

[1072] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDRIHQQDFVNWLLAQRGRRNDWKHNITQ；

[1073] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDRIHQQDFVNWLLAQRGRKNDWRHNITQ；

[1074] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDRIHQQDFVNWLLAQRGKRNDWRHNITQ；

[1075] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDRIHQQDFVNWLLAQKGRRNDWRHNITQ；

[1076] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQRGRRNDWRHNITQ;

[1077] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSKAMDRIHQQDFVNWLLAQRGRRNDWRHNITQ;

[1078] $X_{GI1}X_{GI2}X_{GI3}$GTFISDKSIAMDRIHQQDFVNWLLAQRGRRNDWRHNITQ;

[1079] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDRIHQQDFVNWLLAQRPSSGAPPPSK;

[1080] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDRIHQQDFVNWLLAQRPSSGAPPPK-NH_2;

[1081] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDRIHQQDFVNWLLAQKPSSGAPPPS-NH_2;

[1082] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQRPSSGAPPPS-NH_2;

[1083] $X_{GI1}X_{GI2}X_{GI3}$GTFISDKSIAMDRIHQQDFVNWLLAQRPSSGAPPPS-NH_2;

[1084] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDRIHQQDFVNWLLAQK-NH_2;

[1085] $X_{GI1}X_{GI2}X_{GI3}$GTFISDYSIAMDKIHQQDFVNWLLAQR-NH_2;

[1086] FISDYSIAMDRIHQQDFVNWLLAQK-NH_2;

[1087] FISDYSIAMDKIHQQDFVNWLLAQR-NH_2;

[1088] ISDYSIAMDRIHQQDFVNWLLAQK-NH_2;或者,

[1089] ISDYSIAMDKIHQQDFVNWLLAQR-NH_2;

[1090] 各变量如本中所定义的;

[1091] GIP受体结合多肽通过赖氨酸侧链的氨基与连接基的N-羟基琥珀酰亚胺酯反应,进而连接到白介素-1受体拮抗蛋白。

[1092] 在一个实施方式中,融合蛋白的序列为:

[1093] (GIP-1受体结合多肽-连接基)-C_{IL0}-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE,各变量如本文中所定义的。

[1094] 在一种实施方式中,连接基有一个醛基,通过还原性胺化与白介素-1受体拮抗蛋白N末端连接;在另外一种实施方式中,C_{IL0}半胱氨酸通过侧链巯基与连接基连接,再连接GIP受体结合多肽。

[1095] 在一个实施方式中,所述融合蛋白的序列为:

[1096] U_L-X_{IL0}RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVX$_{IL84}$ITDLSENRKQDKRFAFIRSDSGPTTSFESAAX$_{IL116}$PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDEC$_{IL153}$(连接基-GIP受体结合多肽),各变量如本文中所定义的。

[1097] GIP受体结合多肽一般可以通过氨基酸残基侧链的氨基或巯基与连接基反应。

[1098] 在一种实施方式中,胰岛素受体结合多肽是经过修饰的缀合物。

[1099] GIP受体结合多肽和白介素-1受体拮抗蛋白的二聚蛋白/交联蛋白序列选自:

[1100] GI-24:

[1101] MRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GIP受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNM PDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:178);其中GIP受体结合多肽的序列是:

[1102] Ac-YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWCHNITQ(SEQ ID NO:197),通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体结合蛋白;

[1103] GI-25:

[1104] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG40K-马来酰亚胺-S-GIP受体结合多肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:179);其中GIP受体结合多肽的序列是:

[1105] Ac-YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQC(SEQ ID NO:198),通过C末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体结合蛋白;GI-26:

[1106] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG40K-马来酰亚胺-S-GIP受体结合多肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:180);其中GIP受体结合多肽的序列是:

[1107] YAPGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQC(SEQ ID NO:199),通过C末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体结合蛋白;

[1108] GI-27:

[1109] MRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDEC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GIP受体结合多肽)(S是半胱氨酸侧链的硫原子)(SEQ ID NO:181);其中GIP受体结合多肽的序列是YAibEGTFISDYSIAMDKIHQQDFVNWLLAQC-NH_2(SEQ ID NO:200);

[1110] GI-28:

[1111] C(S-马来酰亚胺-PEG11-马来酰亚胺-S-GIP受体结合多肽)RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC[S-CH_2-CONH-$(CH_2CH_2O)_4$-$(CH_2)_2$-NH-(N^{α}-(HOOC$(CH_2)_{16}$CO)-γ-Glu)]PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:182);其中GIP受体结合多肽的序列是YAibEGTFISDYSIAMDKIHQQDFVNWLLAQKPSSGAPPPSC(SEQ ID NO:201),通过C末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体结合蛋白;

[1112] GI-29:

[1113] MRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVC(S-马来酰亚胺-PEG40K-马来酰亚胺-S-GIP受体结合多肽)ITDLSENRKQDKRFAFIRSDSGPTTSFESAASPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:183);其中GIP受体结合多肽的序列是Ac-YAEGTFISDYSIAMDKIHQQDFVNWLLAQKPSSGAPPPC-NH_2(SEQ ID NO:202),通过C末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体结合蛋白;

[1114] GI-30:

[1115] RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAAC(S-马来酰亚胺-PEG11-马来酰亚胺-S-GIP受体结合多肽)PGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE(S是半胱氨酸侧链的硫原子)(SEQ ID NO:184);其中GIP受体结合多肽的序列是FISDYSIAMDKIHQQDFVNWLLAQKC-NH_2(SEQ ID NO:203),通过C末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体

结合蛋白。

[1116] 药物组合物及用途

[1117] 在本发明的另一方面中，提供了一种药物组合物，所述药物组合物包括治疗有效量的根据本发明的融合蛋白或其缀合物和制药学上可接受的载体或添加剂，可选地包括其它糖尿病的化合物，用于治疗1型糖尿病、2型糖尿病和引起高血糖症的其它情况。根据本发明的融合蛋白可以用于治疗1型糖尿病、2型糖尿病和引起高血糖症的其它情况的药物组合物的制备。

[1118] 可以使用制药工业的常规技术制备本发明的融合蛋白的可注射组合物，包括溶解和混合适当组分而得到所需终产品。因此，按照一套操作步骤，将本发明的融合蛋白溶于一定量的水，其体积稍低于待制备的组合物的最终体积。如果需要，加入防腐剂、等渗剂和缓冲剂。如果有必要，使用酸(例如盐酸)或碱(例如氢氧化钠)调节溶液的pH。最终用水将溶液的体积调节到所需浓度。

[1119] 在本发明的另一个实施方案中，缓冲剂选自乙酸钠、碳酸钠、柠檬酸盐、甘氨酰甘氨酸、组氨酸、甘氨酸、赖氨酸、精氨酸、磷酸二氢钠、磷酸氢二钠、磷酸钠和三(羟甲基)-氨基甲烷、N-二(羟乙基)甘氨酸、N-(羟甲基)甲基甘氨酸、苹果酸、琥珀酸盐、马来酸、富马酸、酒石酸、天冬氨酸或其混合物。这些具体缓冲剂中的每一种构成了本发明的备选实施方案。

[1120] 在本发明的另一个实施方案中，防腐剂选自苯酚、邻-甲酚、间-甲酚、对-甲酚、对羟基苯甲酸甲酯、对羟基苯甲酸乙酯、对羟基苯甲酸丙酯、对羟基苯甲酸丁酯、2-苯氧基乙醇、苄醇、氯丁醇、硫柳汞、溴硝丙二醇、苯甲酸、咪脲、双氯苯双胍己烷、脱氢醋酸钠、氯甲酚、苄索氯胺、氯苯甘醚或其混合物。防腐剂的浓度为0.1mg/mL-20mg/mL，优选为0.1mg/mL-5mg/mL。在本发明的另一个实施方案中，防腐剂的浓度为5mg/mL-10mg/mL。这些具体防腐剂中的每一种构成了本发明的备选实施方案。在药物组合中应用防腐剂是本领域技术人员众所周知的。参照Remington:The Science and Practice of Pharmacy，第19版，1995。

[1121] 在本发明的另一个实施方案中，所述制剂进一步包括等渗剂，选自盐(例如氯化钠)、糖或糖醇、氨基酸、醛糖醇(例如甘油、丙二醇、1,3-丙二醇、1,3-丁二醇)、聚乙二醇(例如PEG400)或其混合物。任何糖，如单糖、二糖、多糖或水溶性葡聚糖，包括例如果糖、葡萄糖、甘露糖、山梨糖、木糖、麦芽糖、乳糖、蔗糖、海藻糖、葡聚糖、普鲁蓝、糊精、环糊精、可溶性淀粉、羟乙基淀粉和羧甲基纤维素-Na。在一个实施方案中，糖添加剂为蔗糖。将糖醇定义为具有至少一个-OH基团的C4-C8烃，包括例如甘露糖醇、山梨醇、肌醇、半乳糖醇、卫矛醇、木糖醇和阿拉伯糖醇。在一个实施方案中，该糖醇添加剂为甘露糖醇。上述糖类或糖醇类可以单独使用或组合使用。对用量没有固定限制，只要所述糖或糖醇溶于液体制剂而且不会对使用本发明方法获得的稳定化作用产生不良影响即可。在一个实施方案中，糖或糖醇的浓度为1mg/mL-150mg/mL。在另一个实施方案中，等渗剂的浓度为1mg/mL-50mg/mL。在另一个实施方案中，等渗剂的浓度为1mg/mL-7mg/mL。在另一个实施方案中，等渗剂的浓度为8mg/mL-24mg/mL。在另一个实施方案中，等渗剂的浓度为25mg/mL-50mg/mL。这些具体等渗剂中的每一种构成了本发明的备选实施方案。在药物组合物中应用等渗剂是本领域人员众所周知的。参照Remington:The Science and Practice of Pharmacy，第19版，1995。

[1122] 典型的等渗剂为氯化钠、甘露糖醇、二甲亚砜和甘油，典型的防腐剂为苯酚、间-甲酚、对羟基苯甲酸甲酯和苄醇。表面活性剂的实例包括乙酸钠、甘氨酰甘氨酸、羟乙基哌嗪

乙磺酸(HEPES)和磷酸钠。

[1123] 实施例

[1124] 保护基:

[1125] Acm acetamidomethyl:乙酰胺甲基;Alloc或AOC allyloxycarbonyl:烯丙氧羰基;Bom,benzyloxymethyl:苄氧甲基;Br-Z,2-bromobenzyloxycarbonyl:2-溴苄氧羰基;tBu,t-butyl:叔丁基;Bz,benzoyl:苯甲酰基;Bzl,benzyl:苄基;Boc:叔丁氧羰基;CHO formyl:甲酰基;cHx,cyclohexyl:环己基;Cbz或Z benzyloxycarbonyl:苄氧羰基;Cl-Z,2-chlorobenzyloxycarbonyl:2-氯苄氧羰基;Fm,9-fluorenylmethyl:9-芴基甲基;Fmoc,9-fluorenylmethoxycarbonyl:9-芴甲氧羰基;Mtt,4-methyltrityl:4-甲基三苯甲基;Npys,3-nitro-2-pyridinesulfenyl:3-硝基-2-吡啶亚磺酰基;Pmc,(2,2,5,7,8-pentametylchroman-6-sulphonyl:2,2,5,7,8-五甲基-6-羟基色满;Tos,4-toluenesulphonyl:对甲苯磺酰;Trt,tripheylmethyl:三苯甲基;Xan,xanthyl:吨基、氧(杂)蒽基。

[1126] 试剂和溶剂:

[1127] ACN,acetonitrile:乙腈;BOP,benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate:苯并三唑-1-三(三甲氨基)-六氟磷酸酯(卡特缩合剂);DCC,N,N'-Dicyclohexylcarbodiimide:二环己基碳化二亚胺;DCM:二氯甲烷;DEPBT,3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one:3-(二乙氧基邻酰氧基)-1,2,3-苯并三嗪-4-酮;DIC,N,N'-Diisopropylcarbodiimide:N,N'-二异丙基碳二亚胺;DIPEA(或DIEA),diisopropylethylamine:二异丙基乙胺;DMAP,4-N,N-dimethylaminopyridine:4-N,N二甲氨基吡啶;DMF:N,N-二甲基甲酰胺;DMSO:二甲亚砜;DTT,dithiothreitol:二硫苏糖醇;EDC或EDCI,1-ethyl-3-(3-dimethylaminopropyl)carbodiimide:1-乙基-(3-二甲基氨基丙基)碳酰二亚胺盐酸盐;EtOAc:乙酸乙酯;HBTU O-(1H-benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate:苯并三氮唑-N,N,N',N'-四甲基脲六氟磷酸盐;HOBT 1-hydroxybenzotriazole:1-羟基-苯并-三氮唑;Cl-HOBT:6-氯-1-羟基-苯并-三氮唑;NMM,N-Methylmorpholine:N-甲基吗啉;NMP,N-methylpyrrolidinone:N-甲基吡咯烷酮;Piperidine:哌啶;Su succinimide:琥珀酰亚胺;TEA,triethylamine:三乙胺;TFA,trifluoroacetic acid三氟乙酸;TFE 2,2,2-Trifluoroethanol三氟代乙醇;THF tetrahydrofuran四氢呋喃;TIS triisopropylsilane:三异丙基硅烷。

[1128] 若无特殊说明,本发明中使用的试剂均是普通化学试剂商店或生物试剂/制品商店可购买的,或者是本领域常规配制试剂,所述实验及其步骤均是本领域技术人员根据本发明内容和本领域常规技术可以完成的。

[1129] 白介素-1受体拮抗蛋白的开放读码框架序列:

[1130] ATGGAAATCTGCAGAGGCCTCCGCAGTCACCTAATCACTCTCCTCCTCTTCCTGTTCCATTCAGAGACGATCTGCCGACCCTCTGGGAGAAAATCCAGCAAGATGCAAGCCTTCAGAATCTGGGATGTTAACCAGAAGACCTTCTATCTGAGGAACAACCAACTAGTTGCTGGATACTTGCAAGGACCAAATGTCAATTTAGAAGAAAAGATAGATGTGGTACCCATTGAGCCTCATGCTCTGTTCTTGGGAATCCATGGAGGGAAGATGTGCCTGTCCTGTGTCAAGTCTGGTGATGAGACCAGACTCCAGCTGGAGGCAGTTAACATCACTGACCTGAGCGAGAACAGAAAGCAGGACAAGCGCTTCGCC

TTCATCCGCTCAGACAGTGGCCCCACCACCAGTTTTGAGTCTGCCGCCTGCCCCGGTTGGTTCCTCTGCACAGCGATGGAAGCTGACCAGCCCGTCAGCCTCACCAATATGCCTGACGAAGGCGTCATGGTCACCAAATTCTACTTCCAGGAGGACGAGTAG。

[1131] IL-1ra氨基酸序列：

[1132] MEICRGLRSHLITLLLFLFHSETICRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE*。

[1133] 1.白介素-1受体拮抗蛋白的cDNA克隆和表达载体的构建

[1134] 1.1设计引物，包含限制性内切酶酶切位点，用于插入DNA的PCR扩增产物

[1135] 我们用RT-PCR方法从人肝组织中获得IL-1Ra cDNA序列。首先要检查被扩增的cDNA序列，鉴定这些酶切位点不在cDNA上，设计适当的引物，从而特异性地扩增cDNA的5'-端。首先扩增编码完整或成熟的IL-1Ra cDNA序列，用限制性内切酶消化后，与pSUMO载体连接。市场上有多种pSUMO载体，例如Lifesensors、Invitrogen公司的产品，都可以应用于本发明的蛋白。

[1136] 引物设计：

[1137] 正向引物1:5'-GGCGGTCTCTAGGT-ATGGAAATCTGCAGA-3'用于克隆IL-1ra完整序列；

[1138] 正向引物2:5'-GGCGGTCTCTAGGT-CGACCCTCTGGGAGA-3'用于克隆IL-1ra成熟肽序列；

[1139] 在这个序列中，GGTCTC是限制性内切酶Bsal的识别序列。

[1140] 反向引物5'-GGCGGATCCTTA CTACTCGTCCTCCTG-3'；在这个序列中，GGATCC是限制性内切酶BamHI的识别序列。

[1141] 1.2逆转录聚合酶链反应(RT-PCR)

[1142] 首先，用逆转录聚合酶链反应得到人IL-1Ra cDNA。

[1143] 逆转录：

[1144]

肝组织RNA (1μg/μl)	2 微升
寡核苷引物	1 微升
水	2 微升
	5 微升

[1145] 混合，在70℃变性5分钟，然后放置冰上5分钟。

[1146]

10X逆转录缓冲液	2 微升
$MgCl_2$(25mM)	4.4 微升
dNTPs(10mM)	1 微升
水	6.1 微升
RNA酶抑制剂	0.5 微升
逆转录酶	1 微升
	15 微升

[1147] 将以上两者混合，放入PCR机器中进行逆转录反应(25℃5分钟，42℃1小时，70℃15

分钟)。

[1148] PCR反应体系：

[1149]

10X缓冲液	2.5 微升
cDNA模板	0.5 微升
正向引物2 (25μM)	2 微升
反向引物 (25μM)	2 微升
Taq DNA 聚合酶	1 微升
dNTPs(10mM)	0.5 微升
无核酸酶水	16.5 微升
	25 微升

[1150] PCR反应程序

[1151]

步骤1	94℃	5分钟	
步骤2	94℃	30秒	30个循环
步骤3	54℃	30秒	
步骤4	72℃	1分钟	
步骤5	72℃	5分钟	

[1152] 1.3 PCR产物的纯化

[1153] 使用Qiagen DNA凝胶提取试剂盒从琼脂糖凝胶中提取DNA：

[1154] 1.通过1％琼脂糖凝胶电泳PCR产物,使用长波长紫外灯确定预期约为0.5kb的PCR产物条带；

[1155] 2.用干净的刀片切下含有PCR产物的凝胶片；

[1156] 3.称量试管中的凝胶片,加入3体积的缓冲液QX1到1体积的凝胶片中；

[1157] 4.向样品加入20微升QIAEX II；

[1158] 5.在50℃孵育10分钟以溶解凝胶和结合DNA；

[1159] 6.样品离心30秒,小心除去上清液；

[1160] 7.用缓冲液QX1洗沉淀物；

[1161] 8.用缓冲液PE洗沉淀物2次；

[1162] 9.空气干燥沉淀物15分钟；

[1163] 10.加入20微升水,震荡以洗脱DNA;室温放置5分钟；

[1164] 11.离心30秒,转移上清液到一个干净的试管中(上清液含有纯化的DNA)。

[1165] 1.4限制性内切酶消化

[1166] 使用BsaI和BamHI内切酶：

[1167]

10X 酶解缓冲液	2.5 微升
BsaI (10单位/微升)	1.5 微升
纯化的PCR产物	21 微升

[1168] 25 微升

[1169] 在50℃酶解1小时；

[1170] 加入0.5微升10X酶解缓冲液(NEB2)、1.5微升BamHI(10单位/微升)、10XBSA(NEB)3微升,在37℃酶解1小时。

[1171] 1.5纯化酶解的DNA产物

[1172] 使用Montage DNA凝胶提取试剂盒#LSKG EL0 50(Millipore)。

[1173] 1.6连接IL-1ra cDNA和pSUMO载体(参照附图1A,1B)

[1174] 1.合并50微克载体(1微升pSUMO载体用4微升无核酸酶纯水稀释,使浓度为50微克/微升)和插入cDNA片段,使总体积为10微升(1微升稀释载体加9微升酶解PCR产物)；

[1175] 2.加入10微升2X连接缓冲液并混合；

[1176] 3.加入1微升T4 DNA连接酶,混合,离心；

[1177] 4.在室温下静置1小时；

[1178] 5.进入转化步骤。

[1179] 1.7大肠杆菌DH5α转化

[1180] 1.在冰上融化大肠杆菌DH5α细胞；

[1181] 2.每次转化使用30微升DH5α细胞悬浊液；

[1182] 3.2微升连接物与30微升DH5α细胞悬浊液混合；

[1183] 4.细胞在冰上放置45分钟；

[1184] 5.在42℃水浴中热休克90秒；

[1185] 6.细胞在冰上放置5分钟；

[1186] 7.加入250微升SOC培养液,37℃、200rpm摇动培养1小时；

[1187] 8.在含有100微克/毫升氨苄西林的LB琼脂平板上平铺100μl细胞悬浊液,在37℃培养过夜。

[1188] 1.8质粒DNA分析

[1189] 1.挑选1-10个菌落,用一个T7正向引物和一个用于扩增特异性IL-1ra基因的反向引物进行克隆PCR以鉴定阳性菌落；

[1190] 2.接种3-5个阳性菌落到5ml含有微克/毫升氨苄西林的肉汤培养液中；

[1191] 3.在37℃250rpm摇动培养过夜；

[1192] 4.提取质粒DNA。

[1193] 1.9质粒DNA测序(参照图2)

[1194] 1.用T7正向引物和pSUMO载体特异的反向引物对提取的质粒DNA进行测序；

[1195] 2.测序后,带有IL-1ra cDNA的pSUMO表达质粒放于-80℃保存,以备转化大肠杆菌OrigamiB(DE3)。

[1196] 2.白介素-1受体拮抗蛋白在大肠杆菌中的表达

[1197] 注:下述的试剂浓度/体积表示为1升培养物体积。

[1198] 2.1大肠杆菌origamiB(DE3)的转化

[1199] 1.在冰上融化20微升大肠杆菌origamiB(DE3)细胞；

[1200] 2.向感受态细胞中加入1μl带有IL-1ra cDNA的pSUMO表达质粒,轻轻搅动,混合；

[1201] 3.试管在冰上放置5分钟；

[1202] 4.在42℃水浴中热休克30秒；

[1203] 5.细胞放置在冰上2分钟；

[1204] 6.加入80微升SOC培养液；

[1205] 7.在37℃孵育1小时；

[1206] 8.在LB/氨苄西林(100微克/毫升)琼脂平板上平铺100微升细胞悬浊液，在37℃孵育过夜。

[1207] 2.2蛋白表达

[1208] 1.培养基制备：准备1升LB培养基，在37℃预热一夜。使用前加入氨苄西林，终浓度为100微克/毫升；

[1209] 2.种子培养：挑选一个好的转化的origamiB(DE3)菌落，接种到含有12.5毫升LB培养基和100微克/毫升氨苄西林的50毫升烧瓶中，在37℃培养过夜；

[1210] 3.制备培养：接种4毫升过夜培养的origamiB(DE3)细胞到1升预热的含有100微克/毫升氨苄西林的LB培养基中；

[1211] 注：甘油菌种储备应该制备并保存在-80℃(400微升培养液和600微升无菌甘油)；

[1212] 在IPTG诱导前、后收集培养液样品，用SDS-PAGE分析蛋白表达情况；

[1213] 4.IPTG诱导：当光学密度OD600达到0.4(大约需要3个小时)，加入48毫克IPTG(异丙基-beta-D-硫代半乳糖苷)诱导蛋白表达(IPTG最终浓度是0.2mM)。然后继续培养3个小时；

[1214] 5.细胞收集：在5500rpm离心10分钟，收集细胞。

[1215] 2.3提取：细胞裂解

[1216] 1.用15毫升Bugbuster蛋白提取试剂重新悬浮细胞；

[1217] 2.加入15微升Benzonase核酸酶和100微升100mg/ml PMSF(蛋白抑制剂)以裂解细胞；

[1218] 3.在室温下旋转孵育15分钟；

[1219] 4.加2毫升细胞裂解物到2毫升微量离心管中；

[1220] 5.在微型离心机以14,000rpm，4℃离心30分钟；

[1221] 6.沉淀物(包合体)溶解在8毫升含有50mM HEPES-NaOH，pH 7.5、6M盐酸胍、25mM DTT中，在4℃放置1小时；

[1222] 7.在4℃，14000rpm离心30分钟以除去不溶物；

[1223] 8.上清液(含有溶解的蛋白)存储在-20℃。

[1224] 2.4 His-Tag纯化

[1225] 使用TALON离心柱(Clontech，#635601，2毫升，每根柱子有2-4毫克的结合力。存放在4℃)；

[1226] 1.使用前，轻敲柱子以使树脂沉入柱子底部；

[1227] 2.柱子置于2毫升微量离心管，除去顶盖，1000rpm离心2分钟；

[1228] 3.加入1毫升平衡缓冲液(50mM磷酸钠、6M盐酸胍、500mM NaCl)，充分悬浮树脂；

[1229] 4.柱子在1000rpm离心2分钟；

[1230] 5.重复平衡步骤；

[1231] 6.每个柱子加入1.5毫升浓缩样品；

[1232] 7.轻敲柱子，使树脂充分悬浮，在4℃旋转柱子5分钟；

[1233] 8.在1000rpm离心2分钟；

[1234] 9.用1毫升洗涤缓冲液(与平衡缓冲液相同)清洗柱子，使树脂充分悬浮，旋转柱子5分钟；

[1235] 10.在1000rpm离心2分钟；

[1236] 11.重复清洗步骤；

[1237] 12.用700微升洗脱缓冲液(50mM磷酸钠、6M盐酸胍、500mM NaCl、150nM咪唑)，在1000rpm离心2分钟，洗脱标记蛋白；

[1238] 13.收集洗脱液。

[1239] 2.5蛋白重折叠

[1240] 1.制备重折叠溶液(50mM HEPES pH7.5、0.2M NaCl、1mM DTT、1M NDSB201)NDSB201是吡啶丙烷磺酸内盐3-(1-pyridine)-1-propene sulfonate；

[1241] 2.按1:5混合纯化的蛋白和重折叠溶液，迅速剧烈震荡30秒；

[1242] 3.在4℃旋转样品1小时；

[1243] 4.样品浓缩和透析。

[1244] 2.6样品浓缩

[1245] 柱子:Amicon Ultra-430kDa cut-off离心过滤机(Millipore,#UFC803024)

[1246] 1.将4毫升样品加到Amicon离心管的上部；

[1247] 2.在4℃，3000rpm离心10分钟，或直到上部的体积达到1毫升；

[1248] 3.收集浓缩样品透析。

[1249] 2.7渗析

[1250] 设备:D-tube Dialyzer Maxi,MWCO 6-8(Novagen,#71509-3)

[1251] 1.向透析器加入2毫升去离子水，在室温放置5分钟，使透析器膜达到平衡；

[1252] 2.去掉水，每个透析器加入2毫升样品；

[1253] 3.关上透析器，放入浮动支架上；

[1254] 4.在4℃，用1升50mM Tris-HCl，500mM NaCl缓冲液透析样品过夜以除去盐酸胍；

[1255] 5.收集透析后的样品；

[1256] 6.除去His-标记前用SDS-PAGE检查蛋白。

[1257] 2.8去除SUMO标记

[1258] 1.向500微升渗析后的IL-1ra中加入5微升SUMO蛋白酶，在37℃孵育1小时；

[1259] 2.用Talon柱除去His-标记；

[1260] 3.向空的1.5毫升微量离心管加入100微升树脂；

[1261] 4.3000rpm离心，除去存储缓冲液；

[1262] 5.加入500微升50mM Tris-HCl，500mM NaCl以悬浮和平衡树脂；

[1263] 6.3000rpm离心，除去平衡缓冲液；

[1264] 7.加入500微升酶切后样品到含有平衡过树脂的离心管中；

[1265] 8.混合树脂和蛋白，在4℃旋转5分钟；

[1266] 9.在3000rpm和4℃离心，分离树脂，收集含有酶切的、分离的IL-1ra的上清液；

[1267] 10.用15％SDS-PAGE分析样品；

[1268] 11.用RP-HPLC分析样品纯度。参照图4。必要时用RP-HPLC纯化样品；

[1269] 12.可以使用质谱分析和肽质量指纹谱确认蛋白序列的正确性。参照图5和图6。

[1270] 胰岛素受体结合多肽-连接基-IL-1Ra cDNA序列(含两个拷贝的连接基)

[1271] TTTGTCAATCAGCACCTTTGTGGTTCTCACCTGGTGGAGGCTCTGTACCTGGTGTGTGGGGAACGTGG
TTTCTTCTACACACCCAAGACCGGCTCGGGCTCGTCGTCGGCTGCTGCTCCCCAGACCGGCATTGTGGAGCAGTGC
TGCACCAGCATCTGCTCCCTCTACCAACTGGAGAACTACTGCAACGGCGGCGGCGGCTCGGGCGGCGGCGGCTCGC
GACCCTCTGGGAGAAAATCCAGCAAGATGCAAGCCTTCAGAATCTGGGATGTTAACCAGAAGACCTTCTATCTGAG
GAACAACCAACTAGTTGCTGGATACTTGCAAGGACCAAATGTCAATTTAGAAGAAAAGATAGATGTGGTACCCATT
GAGCCTCATGCTCTGTTCTTGGGAATCCATGGAGGGAAGATGTGCCTGTCCTGTGTCAAGTCTGGTGATGAGACCA
GACTCCAGCTGGAGGCAGTTAACATCACTGACCTGAGCGAGAACAGAAAGCAGGACAAGCGCTTCGCCTTCATCCG
CTCAGACAGTGGCCCCACCACCAGTTTTGAGTCTGCCGCCTGCCCCGGTTGGTTCCTCTGCACAGCGATGGAAGCT
GACCAGCCCGTCAGCCTCACCAATATGCCTGACGAAGGCGTCATGGTCACCAAATTCACTTCCAGGAGGACGAGT
AG;

[1272] 胰岛素受体结合多肽-连接基-IL-1Ra氨基酸序列(含两个拷贝的连接基)(IN-7):

[1273] FVNQHLCGSHLVEALYLVCGERGFFYTPKTGSGSSSAAAPQTGIVEQCCTSICSLYQLENYCNGGGGS
GGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVK
SGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFY
FQEDE;

[1274] Exendin-4-连接基-IL-1Ra cDNA序列(含两个拷贝的连接基)

[1275] CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAGGCAGTGCGGTTATTTAT
TGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGGGCACCTCCGCCATCGGGCGGCGGCGGCTCGGGCGGCGGCGGC
TCGCGACCCTCTGGGAGAAAATCCAGCAAGATGCAAGCCTTCAGAATCTGGGATGTTAACCAGAAGACCTTCTATC
TGAGGAACAACCAACTAGTTGCTGGATACTTGCAAGGACCAAATGTCAATTTAGAAGAAAAGATAGATGTGGTACC
CATTGAGCCTCATGCTCTGTTCTTGGGAATCCATGGAGGGAAGATGTGCCTGTCCTGTGTCAAGTCTGGTGATGAG
ACCAGACTCCAGCTGGAGGCAGTTAACATCACTGACCTGAGCGAGAACAGAAAGCAGGACAAGCGCTTCGCCTTCA
TCCGCTCAGACAGTGGCCCCACCACCAGTTTTGAGTCTGCCGCCTGCCCCGGTTGGTTCCTCTGCACAGCGATGGA
AGCTGACCAGCCCGTCAGCCTCACCAATATGCCTGACGAAGGCGTCATGGTCACCAAATTCTACTTCCAGGAGGAC
GAGTAG;

[1276] Exendin-4-连接基-IL-1Ra氨基酸序列(含两个拷贝的连接基)(G-3)

[1277] HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGSGGGGSRPSGRKSSKMQAFRIWDVN
QKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQD
KRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE;

[1278] GLP-1受体结合多肽-连接基-IL-1Ra cDNA序列(含两个拷贝的连接基)

[1279] CATGGTGAAGGAACATTTACCAGTGACGTGTCGTCGTACCTCGAGGAGCAGGCTGCTAAGGAGTTTAT
TGCTTGGCTCGTGAAGGGCCGAGGCGGCGGCGGCTCGGGCGGCGGCGGCTCGCGACCCTCTGGGAGAAAATCCAGC
AAGATGCAAGCCTTCAGAATCTGGGATGTTAACCAGAAGACCTTCTATCTGAGGAACAACCAACTAGTTGCTGGAT
ACTTGCAAGGACCAAATGTCAATTTAGAAGAAAAGATAGATGTGGTACCCATTGAGCCTCATGCTCTGTTCTTGGG
AATCCATGGAGGGAAGATGTGCCTGTCCTGTGTCAAGTCTGGTGATGAGACCAGACTCCAGCTGGAGGCAGTTAAC
ATCACTGACCTGAGCGAGAACAGAAAGCAGGACAAGCGCTTCGCCTTCATCCGCTCAGACAGTGGCCCCACCACCA
GTTTTGAGTCTGCCGCCTGCCCCGGTTGGTTCCTCTGCACAGCGATGGAAGCTGACCAGCCCGTCAGCCTCACCAA

TATGCCTGACGAAGGCGTCATGGTCACCAAATTCTACTTCCAGGAGGACGAGTAG;

[1280] GLP-1受体结合多肽-连接基-IL-1RA氨基酸序列(含两个拷贝的连接基)(G-20)

[1281] HGEGTFTSDVSSYLEEQAAKEFIAWLVKGRGGGGSGGGGSRPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE。

[1282] GLP-1受体结合多肽-连接基-IL-1Ra融合基因的构建和融合蛋白的表达

[1283] 用GLP-1和IL-1Ra的特异性引物(P1,GLP-1正向引物:5'-GGCGGTCTCTAGGTCATGGTGAAGGAACATTTA-3';P2,GLP-1反向引物5'-CAGAGGGTCGCGAGCCGCCGCCGCCCGAGCCGCCGCCGCCTCGGCCCTTCACGA GCC A-3';P3,IL-1Ra正向引物5'-GGCCGAGGCGGCGGCGGCTCGGGCGGCGGCGGCTCGCGACCCTCTGGGAGAAAA-3';P4,IL-1Ra反向引物5'-GGCGGATCCCTACTCGTCCTCCTGGAAGTAGAATTT G-3'以及带有GLP-1和IL-1Ra基因的质粒作为模板,用PCR方法分别扩增得到编码GLP-1和IL-1Ra的cDNA片段。在P1和P4引物中分别引入Bsal和BamHI的限制性酶切位点。引物P2和P3有一个46碱基对的互补区域,在这个区域含有编码10个肽的连接基。用P1和P4引物和以上两种PCR产物作为模板,用重叠PCR方法扩增得到编码GLP-1和IL-1Ra的融合基因。GLP-1和IL-1Ra的融合基因由两个拷贝的连接基GGGGS连接,然后GLP-1和IL-1Ra的融合基因用限制性内切酶Bsal和BamHI消化后,与同样用Bsal和BamHI消化的pSUMO载体相连接,得到重组的含有GLP-1和IL-1Ra的融合基因的表达质粒。表达质粒经序列检查后转化大肠杆菌OrigamiB(DE3)表达GLP-1和IL-1Ra的融合蛋白。这种表达质粒的构建和大肠杆菌OrigamiB的转化以及融合蛋白的表达和纯化均与白介素1-受体拮抗剂基因的克隆和表达方法相同。

[1284] 胰岛素受体结合多肽-连接基-IL-1Ra、GIP受体结合多肽-连接基-IL-1Ra和Exendin-4-连接基-IL-1Ra融合基因的构建以及表达与GLP-1受体结合多肽-连接基-IL-1Ra融合基因的构建和融合蛋白表达的策略相同。

[1285] 本发明中的引物用寡聚核苷酸合成仪合成。GLP-1受体结合多肽、GIP受体结合多肽、Exendin-4类似物、胰岛素受体结合多肽、白介素-1受体拮抗蛋白甚至本发明全长融合蛋白的cDNA都可以化学合成。国内外很多生物技术公司提供全基因合成服务。天然人白蛋白和IL-1Ra的cDNA基因序列可以使用RT-PCR方法从人肝组织中获取。此外,人白蛋白和IL-1Ra的cDNA可以从多家商业公司购买,如Origene,Sino Biological Inc.等。人白蛋白的cDNA和表达方法还可以参照文献(Lawn等,"The sequence of human serum albumin cDNA and its expression in E.coli."Nucleic Acids Res.1981,9(22):6103-6114)。IL-1Ra的cDNA和表达方法可以参照文献(Eisenberg等,"Primary structure and functional expression from complementary DNA of a human interleukin-1receptor antagonist."Nature,1990,343:341-346)。

[1286] 人白蛋白cDNA序列

[1287] GATGCAC ACAAGAGTGA GGTTGCTCAT CGGTTTAAAG ATTTGGGAGA

[1288]

AGAAAATTTC AAAGCCTTGG TGTTGATTGC CTTTGCTCAG TATCTTCAGC
AGTGTCCATT TGAAGATCAT GTAAAATTAG TGAATGAAGT AACTGAATTT
GCAAAAACAT GTGTTGCTGA TGAGTCAGCT GAAAATTGTG ACAAATCACT
TCATACCCTT TTTGGAGACA AATTATGCAC AGTTGCAACT CTTCGTGAAA
CCTATGGTGA AATGGCTGAC TGCTGTGCAA AACAAGAACC TGAGAGAAAT
GAATGCTTCT TGCAACACAA AGATGACAAC CCAAACCTCC CCCGATTGGT
GAGACCAGAG GTTGATGTGA TGTGCACTGC TTTTCATGAC AATGAAGAGA
CATTTTTGAA AAAATACTTA TATGAAATTG CCAGAAGACA TCCTTACTTT
TATGCCCCGG AACTCCTTTT CTTTGCTAAA AGGTATAAAG CTGCTTTTAC
AGAATGTTGC CAAGCTGCTG ATAAAGCTGC CTGCCTGTTG CCAAAGCTCG
ATGAACTTCG GGATGAAGGG AAGGCTTCGT CTGCCAAACA GAGACTCAAG
TGTGCCAGTC TCCAAAAATT TGGAGAAAGA GCTTTCAAAG CATGGGCAGT
AGCTCGCCTG AGCCAGAGAT TTCCCAAAGC TGAGTTTGCA GAAGTTTCCA
AGTTAGTGAC AGATCTTACC AAAGTCCACA CGGAATGCTG CCATGGAGAT
CTGCTTGAAT GTGCTGATGA CAGGGCGGAC CTTGCCAAGT ATATCTGTGA
AAATCAAGAT TCGATCTCCA GTAAACTGAA GGAATGCTGT GAAAAACCTC
TGTTGGAAAA ATCCCACTGC ATTGCCGAAG TGGAAAATGA TGAGATGCCT
GCTGACTTGC CTTCATTAGC TGCTGATTTT GTTGAAAGTA AGGATGTTTG
CAAAAACTAT GCTGAGGCAA AGGATGTCTT CCTGGGCATG TTTTTGTATG
AATATGCAAG AAGGCATCCT GATTACTCTG TCGTGCTGCT GCTGAGACTT
GCCAAGACAT ATGAAACCAC TCTAGAGAAG TGCTGTGCCG CTGCAGATCC
TCATGAATGC TATGCCAAAG TGTTCGATGA ATTTAAACCT CTTGTGGAAG
AGCCTCAGAA TTTAATCAAA CAAAATTGTG AGCTTTTTGA GCAGCTTGGA
GAGTACAAAT TCCAGAATGC GCTATTAGTT CGTTACACCA AGAAAGTACC
CCAAGTGTCA ACTCCAACTC TTGTAGAGGT CTCAAGAAAC CTAGGAAAAG
TGGGCAGCAA ATGTTGTAAA CATCCTGAAG CAAAAAGAAT GCCCTGTGCA
GAAGACTATC TATCCGTGGT CCTGAACCAG TTATGTGTGT TGCATGAGAA
AACGCCAGTA AGTGACAGAG TCACCAAATG CTGCACAGAA TCCTTGGTGA
ACAGGCGACC ATGCTTTTCA GCTCTGGAAG TCGATGAAAC ATACGTTCCC
AAAGAGTTTA ATGCTGAAAC GTTCACCTTC CATGCAGATA TATGCACACT
TTCTGAGAAG GAGAGACAAA TCAAGAAACA AACTGCACTT GTTGAGCTTG
TGAAACACAA GCCCAAGGCA ACAAAAGAGC AACTGAAAGC TGTTATGGAT
GATTTCGCAG CTTTTGTAGA GAAGTGCTGC AAGGCTGACG ATAAGGAGAC
CTGCTTTGCC GAGGAGGGTA AAAAACTTGT TGCTGCAAGT CAAGCTGCCT
TAGGCTTATA A

[1289] 人白蛋白氨基酸序列

[1290] DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTL
FGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRH
PYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRF

PKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPA
DLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEF
KPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLS
VVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVE
LVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL

[1291] 人白蛋白与以上几种融合基因的连接与构建以及融合蛋白的表达与GLP-1受体结合多肽-连接基-IL-1Ra融合基因构建和蛋白表达的策略相同。

[1292] GIP-连接基-IL-1Ra cDNA序列(含两个拷贝的连接基)

[1293] TACGCGGAAGGGACTTTCATCAGTGACTACAGTATTGCCATGGACAAGATTCACCAACAAGACTTTGTG
AACTGGCTGCTGGCCCAAAAGGGGAAGAAGAATGACTGGAAACACAACATCACCCAGGGCGGCGGCGGCTCGGGCGG
CGGCGGCTCGCGACCCTCTGGGAGAAAATCCAGCAAGATGCAAGCCTTCAGAATCTGGGATGTTAACCAGAAGACCT
TCTATCTGAGGAACAACCAACTAGTTGCTGGATACTTGCAAGGACCAAATGTCAATTTAGAAGAAAAGATAGATGTG
GTACCCATTGAGCCTCATGCTCTGTTCTTGGGAATCCATGGAGGGAAGATGTGCCTGTCCTGTGTCAAGTCTGGTGA
TGAGACCAGACTCCAGCTGGAGGCAGTTAACATCACTGACCTGAGCGAGAACAGAAAGCAGGACAAGCGCTTCGCCT
TCATCCGCTCAGACAGTGGCCCCACCACCAGTTTTGAGTCTGCCGCCTGCCCCGGTTGGTTCCTCTGCACAGCGATG
GAAGCTGACCAGCCCGTCAGCCTCACCAATATGCCTGACGAAGGCGTCATGGTCACCAAATTCTACTTCCAGGAGGA
CGAGTAG

[1294] GIP受体结合多肽-连接基-IL-1RA氨基酸序列(含两个拷贝的连接基)(N末端尚未酰化的GI-4)

[1295] YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQGGGGSGGGGSRPSGRKSSKMQAFRIW
DVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENR
KQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE。

[1296] (2,5-二氧吡咯烷-1-yl)醋酸酯((2,5-dioxopyrrolidin-1-yl)acetate)

[1297] 醋酸(1.5g,25毫摩尔)溶于二氯甲烷(15ml),加入DCC(5.16g,25毫摩尔)和N-羟基丁二酰亚胺(2.88g,25毫摩尔)的二恶烷溶液(5ml),在4℃搅拌过夜,在室温搅拌2小时。过滤混合物,减压蒸发溶剂,加入石油醚(b.p.60-80℃),过滤结晶并在乙酸乙酯中重结晶得到无色针状产物(3.75g,95.5%产率),m.p.131-134℃。

[1298] GIP融合蛋白N末端酰化反应

[1299] 用以上方法制备GIP受体结合多肽-白介素-1受体拮抗蛋白单链融合蛋白。对于需要N末端酰化的融合蛋白,如GI-2～GI-5、GI-13～15、GI-22等,融合蛋白溶于0.01N HCI,溶液用NaOH调节到pH 6.9,加入等摩尔(2,5-二氧吡咯烷-1-yl)醋酸盐,每次加入1/10量,每30分钟加入碱溶液,保持pH6.9。反应搅拌过夜,用RP-HPLC C18柱纯化。缓冲液A:0.1%TFA水溶液,10%乙腈;缓冲液B:0.1%TFA水溶液,80%乙腈。

[1300] 以上述方法制备GLP-1受体结合多肽-白介素-1受体拮抗蛋白单链融合蛋白,利用质谱检测分子的分子量,通过测序检测制备的单链多肽的结构以验证所合成的化合物,其结果为:

[1301] G-1:分子量计算值21296.0,质谱测试分子量21298.3,测序结果与本申请所示序列一致;

[1302] G-2:分子量计算值21611.3,质谱测试分子量21613.4,测序结果与本申请所示序

列一致；

[1303] G-3:分子量计算值21926.5,质谱测试分子量21928.1,测序结果与本申请所示序列一致；

[1304] G-4:分子量计算值22241.8,质谱测试分子量22243.2,测序结果与本申请所示序列一致；

[1305] G-5:分子量计算值20518.1,质谱测试分子量20520.6,测序结果与本申请所示序列一致；

[1306] G-6:分子量计算值20719.3,质谱测试分子量20721.0,测序结果与本申请所示序列一致；

[1307] G-7:分子量计算值21034.6,质谱测试分子量21035.8,测序结果与本申请所示序列一致；

[1308] G-8:分子量计算值21349.9,质谱测试分子量21351.7,测序结果与本申请所示序列一致；

[1309] G-18:分子量计算值20522.1,质谱测试分子量20524.3,测序结果与本申请所示序列一致；

[1310] G-19:分子量计算值20780.3,质谱测试分子量20781.8,测序结果与本申请所示序列一致；

[1311] G-20:分子量计算值21095.6,质谱测试分子量21098.0,测序结果与本申请所示序列一致；

[1312] G-21:分子量计算值21410.9,质谱测试分子量21412.4,测序结果与本申请所示序列一致；

[1313] G-22:分子量计算值21873.5,质谱测试分子量21875.6,测序结果与本申请所示序列一致；

[1314] G-81:分子量计算值89011.3,质谱测试分子量89013.6,测序结果与本申请所示序列一致；

[1315] G-82:分子量计算值88958.2,质谱测试分子量88960.1,测序结果与本申请所示序列一致；

[1316] G-83:分子量计算值89011.3,质谱测试分子量89013.0,测序结果与本申请所示序列一致；

[1317] G-84:分子量计算值88958.2,质谱测试分子量88960.5,测序结果与本申请所示序列一致。

[1318] 以上述方法制备基于胰岛素受体结合多肽-白介素-1受体拮抗蛋白融合蛋白,利用质谱检测分子的分子量,通过测序检测制备的单链多肽的结构以验证所合成的化合物,其结果为：

[1319] IN-1:分子量计算值23900.0,质谱测试分子量23902.8,测序结果与本申请所示序列一致；

[1320] IN-2:分子量计算值23884.0,质谱测试分子量23886.7,测序结果与本申请所示序列一致；

[1321] IN-3:分子量计算值23835.8,质谱测试分子量23837.2,测序结果与本申请所示序

列一致；

[1322] IN-4:分子量计算值24215.3,质谱测试分子量24317.5,测序结果与本申请所示序列一致；

[1323] IN-5:分子量计算值24199.2,质谱测试分子量24151.3,测序结果与本申请所示序列一致；

[1324] IN-6:分子量计算值24151.1,质谱测试分子量24153.7,测序结果与本申请所示序列一致；

[1325] IN-7:分子量计算值24530.6,质谱测试分子量24532.4,测序结果与本申请所示序列一致；

[1326] IN-8:分子量计算值24514.5,质谱测试分子量24517.1,测序结果与本申请所示序列一致；

[1327] IN-9:分子量计算值24466.4,质谱测试分子量24469.0,测序结果与本申请所示序列一致；

[1328] IN-10:分子量计算值24845.9,质谱测试分子量24847.3,测序结果与本申请所示序列一致；

[1329] IN-11:分子量计算值24829.8,质谱测试分子量24830.9,测序结果与本申请所示序列一致；

[1330] IN-12:分子量计算值24781.6,质谱测试分子量24783.0,测序结果与本申请所示序列一致；

[1331] IN-13:分子量计算值23309.3,质谱测试分子量23311.2,测序结果与本申请所示序列一致；

[1332] IN-14:分子量计算值23293.3,质谱测试分子量23295.1,测序结果与本申请所示序列一致；

[1333] IN-15:分子量计算值23245.1,质谱测试分子量23246.8,测序结果与本申请所示序列一致；

[1334] IN-16:分子量计算值23624.6,质谱测试分子量23626.5,测序结果与本申请所示序列一致；

[1335] IN-17:分子量计算值23608.6,质谱测试分子量23610.0,测序结果与本申请所示序列一致；

[1336] IN-18:分子量计算值23560.4,质谱测试分子量23561.7,测序结果与本申请所示序列一致；

[1337] IN-19:分子量计算值23939.9,质谱测试分子量23941.6,测序结果与本申请所示序列一致；

[1338] IN-20:分子量计算值23923.9,质谱测试分子量23925.3,测序结果与本申请所示序列一致；

[1339] IN-21:分子量计算值23875.7,质谱测试分子量23877.2,测序结果与本申请所示序列一致；

[1340] IN-22:分子量计算值24255.2,质谱测试分子量24256.9,测序结果与本申请所示序列一致；

[1341] IN-23:分子量计算值24239.1,质谱测试分子量24241.5,测序结果与本申请所示序列一致;

[1342] IN-24:分子量计算值24191.0,质谱测试分子量24192.6,测序结果与本申请所示序列一致;

[1343] IN-62:分子量计算值24530.6,质谱测试分子量24537.1,测序结果与本申请所示序列一致;

[1344] IN-63:分子量计算值24514.5,质谱测试分子量24525.5,测序结果与本申请所示序列一致;

[1345] IN-64:分子量计算值24466.4,质谱测试分子量24474.7,测序结果与本申请所示序列一致;

[1346] IN-65:分子量计算值24503.6,质谱测试分子量24515.4,测序结果与本申请所示序列一致;

[1347] IN-66:分子量计算值25064.2,质谱测试分子量25073.6,测序结果与本申请所示序列一致;

[1348] IN-67:分子量计算值24933.0,质谱测试分子量24942.0,测序结果与本申请所示序列一致;

[1349] IN-68:分子量计算值91615.4,质谱测试分子量91624.9,测序结果与本申请所示序列一致;

[1350] IN-69:分子量计算值91615.4,质谱测试分子量91627.2,测序结果与本申请所示序列一致;

[1351] IN-70:分子量计算值91730.6,质谱测试分子量91623.3,测序结果与本申请所示序列一致。

[1352] 以上述方法制备基于GIP受体结合多肽-白介素-1受体拮抗蛋白融合蛋白,利用质谱检测分子的分子量,通过测序检测制备的单链多肽的结构以验证所合成的化合物,其结果为:

[1353] GI-1:分子量计算值22423.2,质谱测试分子量22427.0,测序结果与本申请所示序列一致;

[1354] GI-2:分子量计算值22134.0,质谱测试分子量22138.1,测序结果与本申请所示序列一致;

[1355] GI-3:分子量计算值22449.2,质谱测试分子量22456.3,测序结果与本申请所示序列一致;

[1356] GI-4:分子量计算值22764.5,质谱测试分子量22772.4,测序结果与本申请所示序列一致;

[1357] GI-5:分子量计算值23079.8,质谱测试分子量23090.7,测序结果与本申请所示序列一致;

[1358] GI-6:分子量计算值22060.0,质谱测试分子量22068.5,测序结果与本申请所示序列一致;

[1359] GI-7:分子量计算值22375.2,质谱测试分子量22384.6,测序结果与本申请所示序列一致;

[1360] GI-8:分子量计算值22690.5,质谱测试分子量22695.9,测序结果与本申请所示序列一致;

[1361] GI-9:分子量计算值23005.8,质谱测试分子量23009.2,测序结果与本申请所示序列一致;

[1362] GI-10:分子量计算值21381.0,质谱测试分子量21373.4,测序结果与本申请所示序列一致;

[1363] GI-11:分子量计算值22351.0,质谱测试分子量22360.8,测序结果与本申请所示序列一致;

[1364] GI-12:分子量计算值21720.4,质谱测试分子量21724.1,测序结果与本申请所示序列一致;

[1365] GI-13:分子量计算值22407.0,质谱测试分子量22411.5,测序结果与本申请所示序列一致;

[1366] GI-14:分子量计算值22091.7,质谱测试分子量22097.6,测序结果与本申请所示序列一致;

[1367] GI-15:分子量计算值21776.5,质谱测试分子量21782.4,测序结果与本申请所示序列一致;

[1368] GI-16:分子量计算值20750.4,质谱测试分子量20753.9,测序结果与本申请所示序列一致;

[1369] GI-17:分子量计算值20435.1,质谱测试分子量20438.7,测序结果与本申请所示序列一致;

[1370] GI-18:分子量计算值21528.2,质谱测试分子量21534.2,测序结果与本申请所示序列一致;

[1371] GI-19:分子量计算值20609.3,质谱测试分子量20613.3,测序结果与本申请所示序列一致;

[1372] GI-20:分子量计算值21702.5,质谱测试分子量21709.0,测序结果与本申请所示序列一致;

[1373] GI-21:分子量计算值22017.7,质谱测试分子量22025.6,测序结果与本申请所示序列一致;

[1374] GI-22:分子量计算值89218.7,质谱测试分子量89227.1,测序结果与本申请所示序列一致;

[1375] GI-23:分子量计算值89144.7,质谱测试分子量89153.5,测序结果与本申请所示序列一致。

[1376] 多肽化学合成方法

[1377] 线性多肽使用Boc固相多肽合成法或Fmoc固相多肽合成法。如果使用Fmoc化学合成C-末端是羧基的多肽,选用Wang树脂;C-末端是酰胺的多肽选用Rink amide树脂。如果使用Boc化学合成C-末端是羧基的多肽,选用Pam树脂;C-末端是酰胺的多肽选用MBHA树脂。缩合剂和活化剂是DIC和HOBT,其他可选肽键缩合剂包括BOP、HBTU、DEPBT等。氨基酸5倍过量。缩合时间为1小时。

[1378] Fmoc保护基用50％哌啶/DMF脱除。Boc保护基用TFA脱除。肽键缩合反应用茚三酮

(Ninhydrin,2,2-Dihydroxyindane-1,3-dione)试剂监测。

[1379] 使用Fmoc固相多肽合成法时,通用氨基酸及保护基如下:

[1380] Fmoc-Cys(Trt)-OH、Fmoc-Asp(OtBu)-OH、Fmoc-Glu(OtBu)-OH、Fmoc-His(Trt)-OH、Fmoc-Lys(Boc)-OH、Fmoc-Asn(Trt)-OH、Fmoc-Gln(Trt)-OH、Fmoc-Arg(Pmc)-OH、Fmoc-Ser(tBu)-OH、Fmoc-Thr(tBu)-OH、Boc-Trp(Boc)-OH或Fmoc-Tyr(tBu)-OH。

[1381] 如果赖氨酸的侧链氨基用于酰化反应,赖氨酸的侧链氨基可以使用烯丙氧羰基(aloc)保护。肽链合成完毕,脱除烯丙氧羰基可以用四(三苯基膦)钯(0)和37:2:1比例的DCM、冰醋酸和NMM(15mL/g树脂)在氩气环境,室温条件下搅拌2小时。反应后树脂需要用0.5%DIPEA/DMF(10mL),0.5%三水合二乙基二硫代碳酸钠/DMF(3X10mL),1:1DCM:DMF(5X10mL)清洗。赖氨酸的侧链氨基也可以使用4-甲基三苯甲基(Mtt)。树脂悬浮于DCM,加入TFA/TIS/DCM(1:2:97),震荡10分钟。重复2遍后,树脂用DCM,DMF和异丙醇洗涤。

[1382] 固相Fmoc化学合成多肽后,常用的切割试剂是TFA。将干树脂放在一个摇瓶中,加入适当量TFA/TIS/H_2O(95:2.5:2.5,10-25mL/g树脂),盖上盖子,在室温下进行间歇式旋转震荡。2小时后抽滤树脂,以新的TFA清洗树脂2-3次,合并滤液,滴加8-10倍体积的冰乙醚。最后,离心收集沉淀出来的多肽粗品。

[1383] 使用Boc固相多肽合成法时,通用氨基酸和保护基如下:Boc-Cys(4-MeBzl)-OH、Boc-Asp(OcHx)-OH、Boc-Glu(OcHx)-OH、Boc-His(Bom)-OH、Boc-Lys(2-Cl-Z)-OH,Boc-Asn(Xan)-OH、Boc-Arg(Tos)-OH、Boc-Ser(Bzl)-OH、Boc-Thr(Bzl)-OH、Boc-Trp(CHO)-OH和Boc-Tyr(2-Br-Z)-OH。

[1384] 如果赖氨酸的侧链氨基用于合成内酰胺或酰化反应,赖氨酸的侧链氨基可以使用烯丙氧羰基(aloc)保护或Fmoc保护。如果天冬氨酸或谷氨酸的侧链羧基用于内酰胺合成或酰化反应,羧基应该转化为烯丙酯或9-芴基甲基保护。

[1385] 固相Boc化学合成多肽后,对于PAM,MBHA树脂,一般采用HF切割,每0.1毫摩尔树脂加5毫升HF,同时加入对甲苯酚、对巯基苯酚或苯甲醚等试剂,混合物在冰浴条件下搅拌1小时。HF真空抽干后,多肽用冰乙醚沉淀,离心收集沉淀,经过HPLC分离纯化,冷冻干燥得到最后产品。

[1386] 叔丁基十六烷二酰基-L-Glu(OSu)-OtBu制备

[1387] 十六烷二酸5.72g(20毫摩尔)溶解于240mL无水DMF,用冰浴冷却。逐次添加2-甲基-2-丙醇1.48g(20毫摩尔),DIC 2.7g(2.25mL,21.4毫摩尔),HOBT 2.88g(21.4毫摩尔),NMM 2.16g(2.34mL,21.4毫摩尔),DMAP 244mg(2毫摩尔)。混合物在室温下搅拌过夜。加入80mL水,酸化到pH 3,用乙酸乙酯萃取(80mLX3),有机层用0.1N HCl和饱和食盐水洗,硫酸镁干燥后,溶剂减压蒸发得到十六烷二酸一叔丁酯(3.32g,产率47%)。核磁共振数据为^{1}H-NMR($CDCl_3$)δ2.35(t,2H),1.56-1.66(m,4H),1.44(s,9H),1.21-1.35(m,20H)。

[1388] Fmoc-Glu-OtBu 4.25g(10毫摩尔)溶解于30mL DCM,加到3克2-CTC树脂(2-氯三苯甲基氯树脂,sub.1毫摩尔/g),继续加入DIPEA 1.29g(10毫摩尔,1.74mL)。混合物在摇动器振动5分钟后,再加入DIPEA 1.93g(15毫摩尔,2.6mL)。混合物剧烈振动1小时。树脂中加入2.4mL HPLC级甲醇,混合15分钟。树脂过滤,用DCM(3X30mL)、DMF(2X30mL)、DCM(3X30mL)、甲醇(3X30mL)清洗后,在真空中干燥。

[1389] 用哌啶脱除Fmoc后,3g树脂(3毫摩尔)与十六烷二酸一叔丁酯3.43g(10毫摩尔)加

入50mL无水DMF，逐次加入DIC 1.35g(1.12mL，10.7毫摩尔)、HOBT 1.44g(10.7毫摩尔)、DIPEA 1.3g(10毫摩尔，1.74mL)。在室温振动过夜后，树脂用DMF(2X30mL)和DCM(2X30mL)清洗。

[1390] 准备AcOH/TFE/DCM(1:1:8)的切割液(20mL/g树脂)。树脂悬浮在一半的切割液，室温下放置30分钟。过滤树脂，用另一半切割液洗涤树脂三次。混合滤液加入15倍体积的正己烷，旋蒸去除多余醋酸，得到叔丁基十六烷二酰基-L-Glu-OtBu。^{1}H-NMR($CDCl_3$):δ6.25(d,1H),4.53(m,1H),2.42(m,2H),2.21(m,4H),1.92(m,1H),1.58(m,4H),1.47(s,9H),1.22-1.43(m,18H)。

[1391] 叔丁基十六烷二酰基-L-Glu-OtBu 1g(1.9毫摩尔)溶于5mL无水DMF/DCM(1mL:4mL).加入DCC 0.412g(2毫摩尔)和N-羟基琥珀酰亚胺0.23g(2毫摩尔)。混合物在室温搅拌过夜。过滤混合物，滤液用乙酸乙酯稀释，用0.1N HCl和饱和食盐水洗涤，硫酸镁干燥后，减压蒸发得到叔丁基十六烷二酰基-L-Glu(OSu)-OtBu。^{1}H-NMR($CDCl_3$):δ6.17(d,1H),4.60(m,1H),2.84(s,4H),2.72(m,1H),2.64(m,1H),2.32(m,1H),2.20(m,4H),2.08(m,1H),1.6(m,4H),1.47(s,9H),1.43(s,9H),1.20-1.33(m,20H)。

[1392] 叔丁基十八烷二酰基-L-Glu(OSu)-OtBu按同样方法制备。

[1393] 蛋白/多肽酰化(1)

[1394] 室温下将单链胰岛素类似物(10微摩尔)溶于0.01N HCl，滴加0.01NNaOH至pH7。叔丁基十六烷二酰基-L-Glu(OSu)-OtBu(12微摩尔)溶于乙腈(2mL)，加入多肽溶液。搅拌30分钟后，用50％醋酸酸化，上RP-HPLC C5柱纯化。缓冲液A:0.1％TFA水溶液，10％乙腈缓冲液B:0.1％TFA水溶液，80％乙腈。初步纯化冻干后的多肽加入TFA/TIS/H_2O(95:2.5:2.5,10mL)，30分钟后减压蒸发溶剂，将粗产品溶于缓冲液A并冷冻干燥。使用RP-HPLC C5柱纯化，缓冲液A:0.1％TFA水溶液，10％乙腈缓冲液B:0.1％TFA水溶液，80％乙腈。酰化的单链胰岛素类似物溶于100mM Na_2CO_3(2mL)，加入马来酰亚胺-PEG12-NHS(12微摩尔)，搅拌30分钟后，加入白介素-1受体拮抗蛋白(11微摩尔)。搅拌5小时后，用50％醋酸酸化，上RP-HPLC C5柱纯化。缓冲液A:0.1％TFA水溶液，10％乙腈缓冲液B:0.1％TFA水溶液，80％乙腈。

[1395] 以上述方法制备基于胰岛素受体结合多肽-白介素-1受体拮抗蛋白融合蛋白，利用质谱检测分子的分子量，其结果为：

[1396] IN-33:分子量计算值25135.4，质谱测试分子量25136.9，测序结果与本申请所示序列一致；

[1397] IN-34:分子量计算值25108.4，质谱测试分子量25110.5，测序结果与本申请所示序列一致。

[1398] 18-马来酰亚胺硬脂酸(18-maleimidooctadecanoic acid)制备

[1399] 18-羟基硬脂酸甲酯(4.5g,14.3毫摩尔)溶于50ml二氯甲烷，加入吡啶(4.53g,57.2毫摩尔)，冰浴冷却，用1小时缓缓加入对甲苯磺酰氯(p-toluenesulfonyl chloride)(5.46g,28.6毫摩尔)。反应在4℃搅拌16小时后，依次用1N盐酸水溶液、水、饱和碳酸氢钠、水、饱和食盐水洗，干燥，减压浓缩，用硅胶柱纯化(洗提液是苯)后得到18-磺酰氧基硬脂酸甲酯(5.69g,85％)。m.p.67.5-68.5℃。

[1400] ^{1}H-NMR($CDCl_3$,270MHz):δ1.09-1.42(m,26H),1.53-1.72(m,4H),2.30(t,2H),2.45(s,3H),3.68(s,3H),4.03(t,2H),7.35(d,2H),7.79(d,2H)。

[1401] 邻苯二甲酰亚胺钾盐(potassium phthalimide)(2.96g,16.0毫摩尔)和100ml无水DMF加热到110℃,滴加80ml溶于DMF的18-磺酰氧基硬脂酸甲酯(5.0g,10.7毫摩尔),混合物在110℃搅拌2小时。倒入冰水,总体积达到1.2升,搅拌30分钟。过滤沉淀,溶于氯仿,用水和饱和食盐水洗,用硫酸镁干燥,减压浓缩,用硅胶柱纯化(洗提液:苯:二氯甲烷2:1),得到methyl 18-phtahlimideocatadecanoate(4.15g,88%)。m.p.82-83℃。

[1402] ^{1}H-NMR($CDCl_3$,270MHz):δ1.09-1.42(m,26H),1.53-1.76(m,4H),2.30(t,2H),3.66,3.67(s,t,5H),7.71(m,2H),7.84(m,2H)。

[1403] methyl 18-phthalimideoctadecanoate(2.0g,4.51毫摩尔)、30ml乙醇和80%水合肼(0.42ml,6.76毫摩尔)加热回流9小时。加入6N盐酸(11.3ml,67.6毫摩尔)加热回流1小时。过滤除去不溶固体,滤液减压浓缩。加入30ml乙醇,18.1ml 1N氢氧化钠溶液加热回流18小时。反应用6N盐酸中和,沉淀过滤收集,在乙醇-醋酸-水中重结晶得18-氨基硬脂酸(800mg,59%)。m.p.172°-174℃。

[1404] IR(cm^{-1}):2920,2850,1640,1535,1470,1400FD-MS(m/z):$[M+H]^+$300

[1405] 18-氨基硬脂酸(400mg,1.33毫摩尔)在40℃溶于50ml乙醇和25ml 1N氢氧化钠,在同样温度用2小时缓缓加入马来酸酐(maleic anhydride)(1.97g,20.0毫摩尔)。反应搅拌30分钟,用盐酸酸化,沉淀离心、过滤后,用水洗后减压干燥得到N-(17-carboxyheptadecyl)马来酰胺酸(436mg,88%)。m.p.144°-147.5℃。

[1406] IR(cm^{-1}):3305,2920,2850,1710,1630,1585,1470,1400,1280,1250,1230,1215,1195,1180

[1407] FD-MS(m/z):$[M+H]^+$398

[1408] N-(17-carboxyheptadecyl)马来酰胺酸(400mg,1.01毫摩尔),2.83ml乙酸酐和无水醋酸钠(41.0rag,0.50毫摩尔)加热到100℃,用搅拌1小时。反应冷却后加冰继续搅拌1小时。用氯仿萃取,有机层用水、饱和食盐水洗,无水硫酸镁干燥后减压浓缩,用硅胶柱纯化(洗提液:苯:氯仿1:1)得到18-马来酰亚胺硬脂酸(172mg,45%)。m.p.101-103℃。

[1409] ^{1}H-NMR($CDCl_3$,270MHz):δ1.14-1.40(m,26H),1.48-1.72(m,4H),2.35(t,2H),3.50(t,2H),6.68(s,2H)

[1410] IR(cm^{-1}):2920,2850,1710,1470,1450,1410,840,700FD-MS(m/z):$[M+H]^+$380

[1411] 蛋白/多肽酰化(2):18-马来酰亚胺硬脂酸修饰融合蛋白

[1412] 3ml融合蛋白(3mg)水溶液和0.8ml 0.5M Tris-HCl缓冲液(pH 9)混合,缓缓加入18-马来酰亚胺硬脂酸(1.1摩尔比),反应在室温搅拌过夜。反应过滤,滤液加入SephadexG-25(洗提液:10mM碳酸氢铵溶液),收集大分子量的部分,再用DEAE-Sepharose FastFlow离子交换柱纯化(洗提液:10mM Tris-HCl(pH 8)和0.075M氯化钠溶液),收集的产品再用Sephadex G-25脱盐(洗提液:10mM碳酸氢铵溶液),冷冻干燥后得到产品。

[1413] 以上述方法制备基于GLP-1受体结合多肽-白介素-1受体拮抗蛋白融合蛋白,利用质谱检测分子的分子量,其结果为:

[1414] G-30:分子量计算值22278.0,质谱测试分子量22279.5,与本申请所示化合物一致;

[1415] G-31:分子量计算值22306.0,质谱测试分子量22307.8,与本申请所示化合物一致;

[1416] G-36:分子量计算值22251.0,质谱测试分子量22252.9,与本申请所示化合物一致;

[1417] G-38:分子量计算值22306.0,质谱测试分子量22307.2,与本申请所示化合物一致;

[1418] G-40:分子量计算值21534.2,质谱测试分子量21535.6,与本申请所示化合物一致;

[1419] G-42:分子量计算值21448.1,质谱测试分子量21449.3,与本申请所示化合物一致;

[1420] G-49:分子量计算值21447.1,质谱测试分子量21448.4,与本申请所示化合物一致。

[1421] 以上述方法制备基于胰岛素受体结合多肽-白介素-1受体拮抗蛋白融合蛋白,利用质谱检测分子的分子量,其结果为:

[1422] IN-28:分子量计算值24264.4,质谱测试分子量24266.1,与本申请所示化合物一致。

[1423] 16-(1-叔丁氧基-5-(4-(2,5-二氧-2,5-二氢-1H-吡咯-1-基)丁氨基)-1,5-二氧戊基-2-yl氨基)-16-氧代十六烷酸(16-(1-tert-butoxy-5-(4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)butylamino)-1,5-dioxopentan-2-ylamino)-16-oxohexadecanoic acid)制备。

[1424] 单Boc-丁二胺(N-叔丁氧羰基-1,4-丁二胺)(1.88g,10毫摩尔)和马来酸酐(maleic anhydride)(1.22g,12.5毫摩尔)溶于无水CH_2Cl_2(30ml),室温搅拌2小时,过滤收集白色沉淀,用CH_2Cl_2洗后真空干燥,直接用于下步反应。(Z)-4-(4-(叔丁氧基羰基氨基)丁氨基)-4-oxobut-2-丁烯酸(2.4g,8.4毫摩尔)、乙酸酐(20ml)和无水醋酸钠(1g,12.2毫摩尔)在140℃搅拌6小时,混合物倒入冰水,用氯仿萃取,有机层用水、饱和食盐水洗,无水硫酸镁干燥后减压浓缩,用硅胶柱纯化(正己烷:乙酸乙酯=100/0:50/50v/v),得到白色固体叔丁基4-(2,5-二氧代-2,5-二氢-1H-吡咯-1-yl)氨基甲酸丁酯(1.71g,6.4毫摩尔)。1H NMR(300MHz,CDCl3):δ=6.68(s,2H,CH=CH),4.50(br,1H,NHtBoc),3.50(t,2H,CH2N),3.08(q,2H,CH2NHtBoc),1.60-1.25(m,13H,CH2)。

[1425] 叔丁基4-(2,5-二氧代-2,5-二氢-1H-吡咯-1-yl)氨基甲酸丁酯溶于4N HCl/二恶烷,室温搅拌1小时,减压蒸发除去溶剂,得到1-(4-氨基丁基)-1H-吡咯-2,5-二酮。室温下将1-(4-氨基丁基)-1H-吡咯-2,5-二酮(1g,6毫摩尔)溶于100mM Na_2CO_3(1mL,pH 8)和乙腈(2mL)。叔丁基十六烷二酰基-L-Glu(OSu)-OtBu(4.09g,7.2毫摩尔)溶于乙腈(4mL),搅拌30分钟后,用50%醋酸酸化,上RP-HPLC C5柱纯化,得到16-(1-叔丁氧基-5-(4-(2,5-二氧-2,5-二氢-1H-吡咯-1-基)丁氨基)-1,5-二氧戊基-2-yl氨基)-16-氧代十六烷酸。

[1426] 蛋白/多肽酰化(3)

[1427] 融合蛋白与等摩尔16-(1-叔丁氧基-5-(4-(2,5-二氧-2,5-二氢-1H-吡咯-1-基)丁氨基)-1,5-二氧戊基-2-yl氨基)-16-氧代十六烷酸溶于PBS,多肽浓度10mM。反应在室温进行1小时,用HPLC纯化。缓冲液A:0.1%TFA水溶液,10%乙腈;缓冲液B:0.1%TFA水溶液,80%乙腈。初步纯化冻干后的多肽加入TFA/TIS/H_2O(95:2.5:2.5,10mL),30分钟后真空蒸发溶剂,将粗产品溶于缓冲液A并冻干。使用RP-HPLC C5柱纯化,缓冲液A:0.1%TFA水溶液,

10％乙腈;缓冲液B:0.1％TFA水溶液,80％乙腈。

[1428] 以上述方法制备基于GLP-1受体结合多肽-白介素-1受体拮抗蛋白融合蛋白,利用质谱检测分子的分子量,其结果为:

[1429] G-9:分子量计算值22177.0,质谱测试分子量22179.5,与本申请所示化合物一致;G-12:分子量计算值22465.2,质谱测试分子量22467.1,与本申请所示化合物一致;

[1430] G-14:分子量计算值21258.0,质谱测试分子量21259.6,与本申请所示化合物一致;

[1431] G-15:分子量计算值22135.9,质谱测试分子量22137.3,与本申请所示化合物一致;

[1432] G-17:分子量计算值22423.1,质谱测试分子量22424.7,与本申请所示化合物一致;

[1433] G-25:分子量计算值21319.0,质谱测试分子量21320.4,与本申请所示化合物一致;

[1434] G-27:分子量计算值21634.3,质谱测试分子量21636.0,与本申请所示化合物一致;

[1435] G-29:分子量计算值22439.2,质谱测试分子量22441.1,与本申请所示化合物一致。

[1436] 以上述方法制备基于胰岛素受体结合多肽-白介素-1受体拮抗蛋白融合蛋白,利用质谱检测分子的分子量,其结果为:

[1437] IN-25:分子量计算值25096.3,质谱测试分子量25097.5,与本申请所示化合物一致。

[1438] I-CH_2-CONH-$(CH_2CH_2O)_2$-$(CH_2)_2$-NH-(N^{α}-(tBuOOC$(CH_2)_{14}$CO)-γ-Glu-OtBu)制备

[1439] 叔丁基N-[2-[2-(2-氨基乙氧基)乙氧基]乙基]氨基甲酸乙酯(2.48g,10毫摩尔),2-碘代醋酸(2.05g,11毫摩尔),EDC(1.72g,11毫摩尔),HOBT(1.49g,11毫摩尔)溶于无水DMF,在室温下反应过夜。依次用10％盐酸水溶液、水、饱和碳酸氢钠、水、饱和食盐水洗,干燥,减压浓缩,用硅胶柱纯化,得到叔丁基N-[2-[2-[2-[(2-碘乙酰基)氨基]乙氧基]乙氧基]乙基]氨基甲酸酯。叔丁基N-[2-[2-[2-[(2-碘乙酰基)氨基]乙氧基]乙氧基]乙基]氨基甲酸酯溶于4N HCl/二恶烷,室温搅拌1小时,减压蒸发除去溶剂,得到N-[2-[2-(2-氨基乙氧基)乙氧基]乙基]-2-碘代(iodo)-乙酰胺盐酸盐,直接用于下一步反应。室温下N-[2-[2-(2-氨基乙氧基)乙氧基]乙基]-2-碘代-乙酰胺盐酸盐(1g,2.8毫摩尔)溶于100mM Na_2CO_3(1mL,pH 8)和乙腈(2mL)。叔丁基十六烷二酰基-L-Glu(OSu)-OtBu(1.42g,2.5毫摩尔)溶于乙腈(4mL),搅拌30分钟后,用50％醋酸酸化,上RP-HPLC C5柱纯化,得到最终产物叔丁基16-[[1-叔丁氧羰基-4-[2-[2-[2-[(2-碘代乙酰基)氨基]乙氧基]乙氧基]乙基氨基]-4-氧-丁基]氨基]-16-氧-棕榈酸酯。计算分子量825.4,测量分子量826.9。

[1440] I-CH_2-CONH-$(CH_2CH_2O)_4$-$(CH_2)_2$-NH-(N^{α}-(tBuOOC$(CH_2)_{16}$CO)-γ-Glu-OtBu)用类似方法制备。

[1441] 蛋白/多肽酰化(4)

[1442] 融合蛋白与等摩尔I-CH_2-CONH-$(CH_2CH_2O)_2$-$(CH_2)_2$-NH-(N^{α}-(HOOC$(CH_2)_{14}$CO)-γ-Glu-OtBu)溶于50mM Tris·HCl、5mM EDTA,pH 8.0,在室温避光反应90分钟。用HPLC纯化。

缓冲液A:0.1％TFA水溶液,10％乙腈;缓冲液B:0.1％TFA水溶液,80％乙腈。初步纯化冻干后的多肽加入TFA/TIS/H_2O(95:2.5:2.5,10mL),30分钟后真空蒸发溶剂,将粗产品溶于缓冲液A并冻干。使用RP-HPLC C5柱纯化,缓冲液A:0.1％TFA水溶液,10％乙腈;缓冲液B:0.1％TFA水溶液,80％乙腈。

[1443] 以上述方法制备基于GLP-1受体结合多肽-白介素-1受体拮抗蛋白融合蛋白,利用质谱检测分子的分子量,其结果为:

[1444] G-32:分子量计算值22512.3,质谱测试分子量22513.4,与本申请所示化合物一致;

[1445] G-33:分子量计算值22471.3,质谱测试分子量22473.1,与本申请所示化合物一致;

[1446] G-34:分子量计算值22443.2,质谱测试分子量22445.0,与本申请所示化合物一致;

[1447] G-35:分子量计算值22512.3,质谱测试分子量22513.2,与本申请所示化合物一致;

[1448] G-37:分子量计算值22485.3,质谱测试分子量22487.1,与本申请所示化合物一致;

[1449] G-39:分子量计算值22628.3,质谱测试分子量22630.6,与本申请所示化合物一致;

[1450] G-41:分子量计算值21768.5,质谱测试分子量21770.4,与本申请所示化合物一致;

[1451] G-43:分子量计算值21640.3,质谱测试分子量21642.7,与本申请所示化合物一致;

[1452] G-44:分子量计算值21582.3,质谱测试分子量21583.9,与本申请所示化合物一致;

[1453] G-45:分子量计算值21798.5,质谱测试分子量21800.4,与本申请所示化合物一致;

[1454] G-46:分子量计算值21611.3,质谱测试分子量21612.9,与本申请所示化合物一致;

[1455] G-47:分子量计算值21640.3,质谱测试分子量21642.2,与本申请所示化合物一致;

[1456] G-48:分子量计算值21785.5,质谱测试分子量21787.6,与本申请所示化合物一致;

[1457] G-50:分子量计算值21681.4,质谱测试分子量21682.8,与本申请所示化合物一致。

[1458] 以上述方法制备基于胰岛素受体结合多肽-白介素-1受体拮抗蛋白融合蛋白,利用质谱检测分子的分子量,其结果为:

[1459] IN-26:分子量计算值25089.4,质谱测试分子量25091.6,与本申请所示化合物一致。

[1460] 多肽的聚乙二醇化修饰方法(PEGylation):

[1461] 1、氨基(主链N-末端或赖氨酸侧链)

[1462] a)还原烷基化(reductive alkylation)

[1463] 融合蛋白,mPEG20K-CHO,氰基硼氢化钠($NaBH_3CN$)按1:2:45比例溶于pH 4.3醋酸溶液(0.1M NaCl,0.2M CH_3COOH,0.1M Na_2CO_3)。蛋白浓度为0.5-1mg/mL。反应用HPLC检测和纯化。产率约55%。还原烷基化反应可以将聚乙二醇选择性地结合在多肽的N末端。

[1464] b)NHS酯(N-羟基琥珀酰亚胺)酰化

[1465] 融合蛋白和mPEG20K-NHS按摩尔比1:1溶于0.1N N,N-双(2-羟乙基)甘氨酸溶液(pH 8),蛋白浓度0.5mg/mL。反应在室温进行2小时,用HPLC纯化。产率约90%。

[1466] 2、巯基(半胱氨酸)

[1467] a)PEG-马来酰亚胺

[1468] 融合蛋白与等摩尔mPEG20K-马来酰亚胺溶于PBS(NaCl 150mM,磷酸盐20mM,pH7.5),蛋白浓度3mg/ml。反应在室温进行1小时,用HPLC纯化。产率约90%。

[1469] b)PEG-碘代乙酰胺

[1470] 融合蛋白(3mg/ml)和PEG-碘代乙酰胺(1.5当量)溶于50mM Tris·HCl,5mM EDTA,pH 8.0,在室温避光反应90分钟。未反应的PEG试剂用D-Salt™ Dextran除盐柱清除,再用HPLC纯化。

[1471] 以上述方法制备基于GLP-1受体结合多肽-白介素-1受体拮抗蛋白-PEG融合蛋白,利用质谱检测分子的分子量,其结果为:

[1472] G-10:分子量计算值41584.2,质谱测试得到一宽峰,中间分子量41590.4,与本申请所示化合物一致;

[1473] G-11:分子量计算值41091.7,质谱测试得到一宽峰,中间分子量41097.1,与本申请所示化合物一致;

[1474] G-13:分子量计算值40719.3,质谱测试得到一宽峰,中间分子量40713.6,与本申请所示化合物一致;

[1475] G-16:分子量计算值41926.5,质谱测试得到一宽峰,中间分子量41931.3,与本申请所示化合物一致;

[1476] G-23:分子量计算值40522.1,质谱测试得到一宽峰,中间分子量40530.2,与本申请所示化合物一致;

[1477] G-24:分子量计算值40780.3,质谱测试得到一宽峰,中间分子量40786.1,与本申请所示化合物一致;

[1478] G-26:分子量计算值41095.6,质谱测试得到一宽峰,中间分子量41100.5,与本申请所示化合物一致;

[1479] G-28:分子量计算值41410.9,质谱测试得到一宽峰,中间分子量41413.4,与本申请所示化合物一致。

[1480] 以上述方法制备基于胰岛素受体结合多肽-白介素-1受体拮抗蛋白-PEG融合蛋白,利用质谱检测分子的分子量,结果为:

[1481] IN-27:分子量计算值43939.9,质谱测试得到一宽峰,中间分子量43947.8,与本申请所示化合物一致。

[1482] G-52合成

[1483] IL-1ra与等摩尔的马来酰亚胺-PEG11-马来酰亚胺溶于PBS，多肽浓度5mM。反应在室温进行1小时，再加入等摩尔HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGA PPPC，2小时后用HPLC纯化，缓冲液A:0.1％TFA水溶液，10％乙腈缓冲液B:0.1％TFA水溶液，80％乙腈。化合物分子量计算值22176.9，质谱测试分子量22186.7，测序结果与本申请所示序列一致。

[1484] 以上述方法制备基于GLP-1受体结合多肽-PEG-白介素-1受体拮抗蛋白融合蛋白，利用质谱检测分子的分子量，结果为：

[1485] G-51:分子量计算值22149.9，质谱测试分子量22151.4，与本申请所示化合物一致；

[1486] G-53:分子量计算值21406.1，质谱测试分子量21408.3，与本申请所示化合物一致；

[1487] G-54:分子量计算值21433.1，质谱测试分子量21434.6，与本申请所示化合物一致；

[1488] G-55:分子量计算值21335.0，质谱测试分子量21335.8，是本申请所示化合物；

[1489] G-56:分子量计算值21362.0，质谱测试分子量21364.5，与本申请所示化合物一致；

[1490] G-57:分子量计算值22108.8，质谱测试分子量22110.2，与本申请所示化合物一致；

[1491] G-58:分子量计算值22135.8，质谱测试分子量22137.0，是本申请所示化合物一致；

[1492] G-59:分子量计算值41303.0，质谱测试得到一宽峰，中间分子量41324.5，与本申请所示化合物一致；

[1493] G-60:分子量计算值41330.0，质谱测试得到一宽峰，中间分子量41337.9，与本申请所示化合物一致；

[1494] G-61:分子量计算值40515.2，质谱测试得到一宽峰，中间分子量40522.4，与本申请所示化合物一致；

[1495] G-62:分子量计算值40586.2，质谱测试得到一宽峰，中间分子量40581.3，是本申请所示化合物；

[1496] G-63:分子量计算值40488.1，质谱测试得到一宽峰，中间分子量40478.2，与本申请所示化合物一致；

[1497] G-64:分子量计算值40471.0，质谱测试得到一宽峰，中间分子量40485.6，与本申请所示化合物一致；

[1498] G-65:分子量计算值41261.9，质谱测试得到一宽峰，中间分子量41273.4，与本申请所示化合物一致；

[1499] G-66:分子量计算值41288.9，质谱测试得到一宽峰，中间分子量41295.7，与本申请所示化合物一致；

[1500] G-67:分子量计算值41417.1，质谱测试得到一宽峰，中间分子量41426.8，与本申请所示化合物一致；

[1501] G-70:分子量计算值40629.3，质谱测试得到一宽峰，中间分子量40640.4，是本申请所示化合物；

[1502] G-71:分子量计算值21434.1,质谱测试分子量21435.7,与本申请所示化合物一致;

[1503] G-72:分子量计算值21461.1,质谱测试分子量24163.0,与本申请所示化合物一致;

[1504] G-73:分子量计算值21362.1,质谱测试分子量21363.2,与本申请所示化合物一致;

[1505] G-74:分子量计算值21389.1,质谱测试分子量21391.5,与本申请所示化合物一致;

[1506] G-75:分子量计算值21290.9,质谱测试分子量21292.3,与本申请所示化合物一致;

[1507] G-76:分子量计算值21317.9,质谱测试分子量21319.1,是本申请所示化合物一致;

[1508] G-77:分子量计算值21290.9,质谱测试分子量21292.6,与本申请所示化合物一致;

[1509] G-78:分子量计算值21317.9,质谱测试分子量21319.5,与本申请所示化合物一致;

[1510] G-79:分子量计算值21773.7,质谱测试分子量21775.2,与本申请所示化合物一致;

[1511] G-80:分子量计算值21800.7,质谱测试分子量21801.8,与本申请所示化合物一致。

[1512] G-68合成

[1513] IL-1ra溶于磷酸钠至1mg/ml,pH调为5.0。加入2倍当量的mPEG20K-CHO(结构是$CH_3O-(CH_2CH_2O)_n-(CH_2)_2-CHO$),加入45倍当量氰基硼氢化钠至浓度为1mM。混合物在4℃反应12小时后,用HPLC纯化。PEG20K IL-1ra与等摩尔的马来酰亚胺-PEG11-马来酰亚胺溶于PBS,多肽浓度5mM。反应在室温进行1小时,再加入等摩尔HGEGTFTSDL SKQMEEEAVRLFIEWLKNGGPSSGAPPPC,2小时后用HPLC纯化,缓冲液A:0.1%TFA水溶液,10%乙腈缓冲液B:0.1%TFA水溶液,80%乙腈。化合物分子量计算值42176.9,质谱测试得到一宽峰,中间分子量42193.4,与本申请所示化合物一致。

[1514] 以同样方法制备G-69。

[1515] G-69:分子量计算值41406.1,质谱测试得到一宽峰,中间分子量41424.5,与本申请所示化合物一致。

[1516] 以上述方法制备基于GIP受体结合多肽-PEG-白介素-1受体拮抗蛋白融合蛋白,利用质谱检测分子的分子量,结果为:

[1517] GI-24:分子量计算值23078.0,质谱测试分子量23082.4,与本申请所示化合物一致;

[1518] GI-25:分子量计算值62255.1,质谱测试得到一宽峰,中间分子量62283.5,与本申请所示化合物一致;

[1519] GI-26:分子量计算值62181.1,质谱测试得到一宽峰,中间分子量62217.0,与本申请所示化合物一致;

[1520] GI-27:分子量计算值21712.5,质谱测试分子量21714.6,与本申请所示化合物一致;

[1521] GI-28:分子量计算值23206.2,质谱测试分子量23210.8,与本申请所示化合物一致;GI-29:分子量计算值61598.4,质谱测试得到一宽峰,中间分子量61567.3,与本申请所示化合物一致;

[1522] GI-30:分子量计算值21086.8,质谱测试分子量21089.1,与本申请所示化合物一致。

[1523] 双链胰岛素受体结合多肽的合成

[1524] 文献方法(Han等,"Insulin chemical synthesis using a two-step orthogonal formation of the three disulfides",21st American Peptide Society Symposium,2009)。A链和B链用Fmoc或Boc化学合成方法合成,A7、B7半胱氨酸用通用保护基,但A6、A11、A20和B19半胱氨酸的侧链巯基用Acm保护。合成好的A链和B链从树脂切割下来后变成A-(SH)^{7}(S-Acm)^{6,11,20}和B-(SH)^{7}(S-Acm)^{19}。B链溶于DMF或DMSO,加入等摩尔2,2'-二硫双(5-硝基吡啶)。反应用HPLC检测和纯化,得到B-(S-Npys)^{7}(S-Acm)^{19}。等摩尔A-(SH)^{7}(S-Acm)^{6,11,20}和B-(S-Npys)^{7}(S-Acm)^{19}溶于DMSO,多肽浓度15mg/mL。当A7-B7二硫键形成后,加入80%醋酸水溶液,多肽浓度稀释到1mg/mL。再加入40倍的I_2。反应在室温搅拌1小时后,加入抗坏血酸水溶液终止反应。混合物用HPLC纯化,终产物用质谱确认。

[1525] IN-29合成

[1526] FVNQHLC[1]GSHLVEALYLVC[2]GERGFFYTPRTGKGSSSAAAPQTGIVEQC[3]C[4]TSIC[5]SLYQLENYC[6]N([1]-[6]表示半胱氨酸的编号;所述化合物中通过6个半胱氨酸形成3对二硫键,三对二硫键的具体位置是:C[1]和C[4]形成二硫键,C[2]和C[6]形成二硫键,C[3]和C[5]形成二硫键)(68mg)溶于NH_4HCO_3(15mL,pH 9),加入Mal-dPEG12-NHS(10mg),室温搅拌30分钟后,加入IL-1Ra((175mg),反应在室温下继续搅拌1小时。用HPLC纯化样品,缓冲液A:0.1%TFA水溶液,10%乙腈缓冲液B:0.1%TFA水溶液,80%乙腈。化合物分子量计算值24737.9,质谱测试分子量24739.6。测序结果与本申请所示序列一致。

[1527] 合成A1,B29-diBoc-胰岛素

[1528] 人胰岛素(100mg)溶于水(1mL)和$NaHCO_3$(0.3mL)和DMF(3mL)。加入t-Boc-azide(6mg)。混合物在40°搅拌3小时,加入50%醋酸(0.35mL)终止反应。未反应的t-Boc-azide用乙醚萃取(2X15mL)。水层真空冷冻干燥。粗品含有Boc单取代,双取代和三取代胰岛素。混合物用SP-Sephadex C-25离子交换柱纯化。离子交换柱先用含有6M尿素的1.5M醋酸平衡,多肽洗提流速是48mL/h,线性梯度0.04-0.4M氯化钠/1000mL 6M尿素的1.5M醋酸。Di-t-Boc胰岛素进一步用DEAE-Sephadex A-25柱纯化。色谱柱预先用含有7M尿素的0.01M Tris缓冲液(pH 8.5)平衡。洗提流速35mL/h,梯度0.14-0.28M氯化钠/100mL Tris缓冲液。分子量计算值6007.9,质谱测试分子量6009.2。少量多肽溶于0.05M NH_4HCO_3/20%ACN,用DTT还原10分钟后质谱分析。A(G1-N^{α}-Boc)分子量计算值2483.9,质谱测试分子量2485.1。B(K29-N^{ε}-Boc)分子量计算值3530.1,质谱测试分子量3532.5。胰蛋白酶解后,不含Boc片段的分子量计算值2487.9,质谱测试分子量2488.7;含Boc片段的分子量计算值1060.2,质谱测试分子量1061.3。A1,B29-di-Boc多肽的B1氨基可以与聚乙二醇、白蛋白、脂肪酸等结合形成长效多肽。

[1529] IN-35合成

[1530] A1,B29-diBoc-胰岛素(60mg)溶于DMF(3mL),加入Mal-dPEG12-NHS(9mg)和三乙胺(30μL)。反应在室温下搅拌2小时。减压挥发溶剂后,粗品溶于H_2O/ACN(3:1),用RP-HPLC纯化。分子量计算值6758.8,质谱测试分子量6760.4。马来酰亚胺-diBoc-胰岛素溶于纯净水,多肽浓度10mM。加入IL-1Ra(172mg),在37℃培养30分钟。然后用含有5mM辛酸钠和750mM硫酸铵的20mM磷酸钠溶液稀释。用凝胶过滤层析法除去未反应的试剂,0.05M碳酸氢铵水溶液作为洗脱液。真空冷冻干燥后得到纯品。得到的化合物分子量计算值23884.2,质谱测试分子量23886.7,经分析为Di-Boc IN-35。Di-Boc IN-35溶于TFA/TIS(95:5)(3mL),在室温搅拌15分钟,减压除去溶剂,粗品用RP-HPLC纯化,缓冲液A:0.1%TFA水溶液,10%乙腈缓冲液B:0.1%TFA水溶液,80%乙腈。最终化合物分子量计算值23684.9,质谱测试分子量23887.5,经分析为IN-35。

[1531] 以上述方法制备基于胰岛素受体结合多肽-白介素-1受体拮抗蛋白-PEG融合蛋白,利用质谱检测分子的分子量,其结果为:

[1532] IN-30:分子量计算值24710.9,质谱测试分子量24712.3,与本申请所示化合物一致;

[1533] IN-31:分子量计算值43987.1,质谱测试得到一宽峰,中间分子量43993.5,与本申请所示化合物一致;

[1534] IN-32:分子量计算值43960.1,质谱测试得到一宽峰,中间分子量43972.6,与本申请所示化合物一致;

[1535] IN-35:分子量计算值23684.9,质谱测试分子量23685.2,与本申请所示化合物一致;

[1536] IN-36:分子量计算值23981.3,质谱测试分子量23983.4,与本申请所示化合物一致;

[1537] IN-37:分子量计算值42934.1,质谱测试得到一宽峰,中间分子量42945.8,与本申请所示化合物一致;

[1538] IN-38:分子量计算值23657.9,质谱测试分子量23659.0,与本申请所示化合物一致;

[1539] IN-39:分子量计算值42907.1,质谱测试得到一宽峰,中间分子量42915.6,与本申请所示化合物一致;

[1540] IN-40:分子量计算值23954.3,质谱测试分子量23957.1,与本申请所示化合物一致;

[1541] IN-41:分子量计算值23583.8,质谱测试分子量23585.6,与本申请所示化合物一致;

[1542] IN-42:分子量计算值42833.0,质谱测试得到一宽峰,中间分子量42834.4,与本申请所示化合物一致;

[1543] IN-43:分子量计算值23556.8,质谱测试分子量23559.2,与本申请所示化合物一致;

[1544] IN-44:分子量计算值42806.0,质谱测试得到一宽峰,中间分子量42812.5,与本申请所示化合物一致;

[1545] IN-45:分子量计算值24825.0,质谱测试分子量24826.8,与本申请所示化合物一致;

[1546] IN-46:分子量计算值44074.2,质谱测试得到一宽峰,中间分子量44083.1,与本申请所示化合物一致;

[1547] IN-47:分子量计算值24798.0,质谱测试分子量24799.3,与本申请所示化合物一致;

[1548] IN-48:分子量计算值44047.2,质谱测试得到一宽峰,中间分子量44056.9,与本申请所示化合物一致;

[1549] IN-49:分子量计算值24783.9,质谱测试分子量24785.7,与本申请所示化合物一致;

[1550] IN-50:分子量计算值44033.1,质谱测试得到一宽峰,中间分子量44026.3,与本申请所示化合物一致;

[1551] IN-51:分子量计算值24825.0,质谱测试分子量24827.5,与本申请所示化合物一致;

[1552] IN-52:分子量计算值44074.2,质谱测试得到一宽峰,中间分子量44081.6,与本申请所示化合物一致;

[1553] IN-53:分子量计算值24841.0,质谱测试分子量24843.1,与本申请所示化合物一致;

[1554] IN-54:分子量计算值44090.2,质谱测试得到一宽峰,中间分子量44098.0,测与本申请所示化合物一致;

[1555] IN-55:分子量计算值24135.3,质谱测试分子量24139.2,与本申请所示化合物一致;

[1556] IN-56:分子量计算值24108.3,质谱测试分子量24117.5,与本申请所示化合物一致;

[1557] IN-57:分子量计算值23772.0,质谱测试分子量23773.9,与本申请所示化合物一致;

[1558] IN-58:分子量计算值24068.4,质谱测试分子量24070.7,与本申请所示化合物一致;

[1559] IN-59:分子量计算值23670.9,质谱测试分子量23672.8,与本申请所示化合物一致;

[1560] IN-60:分子量计算值23903.2,质谱测试分子量23891.3,与本申请所示化合物一致;

[1561] IN-61:分子量计算值23802.1,质谱测试分子量23812.6,与本申请所示化合物一致。

[1562] 受体竞争结合分析

[1563] 1.IL-1Ra受体结合分析

[1564] 参照文献(“Interleukin-1receptor antagonist activity of a human interleukin-1inhibitor”,Hannum等,Nature 343,336-340)。简述如下:标准量的比放射性强度(specific Activity)为4000Ci/mmol的^{35}S-标记的IL-1Ra加入96孔板,最终浓度约

等于其K_d(150pM)。小鼠EL4胸腺瘤细胞(ATCC,TIB181,每个细胞约5000个受体)或表达人IL-1受体的中国仓鼠卵巢细胞(每个细胞约30,000个受体)和不同浓度的融合蛋白(从20mM到20pM系列稀释)在4℃培养4小时。细胞用Millipore millititer plate过滤系统收获。保留在过滤膜上的放射性用Ambis radioanalytical imaging system计量。野生型活性的百分比定义为IC_{50}(野生型)/IC_{50}(融合蛋白)。野生型IL-1ra的K_d用Cheng-Prusoff relationship的简化模式估算(K_d=IC_{50}/2),范围在150-400pM,与以前的文献报道一致。

[1565] 2.胰岛素受体结合分析

[1566] (1)^{125}I-胰岛素的制备

[1567] 文献方法(Cresto等,"Preparation of biologically active mono-^{125}I-insulin of high specific activity",Acta Physiol Lat Am.1981,31(1):13-24)

[1568] (2)化合物的受体结合分析

[1569] 文献方法(E.K.Frandsen and R.A.Bacchus."New,simple insulin-receptor assay with universal application to solubilized insulin receptors and receptors in broken and intact cells."Diabetes,1987,36,3:335-340)或下述方法之一。如无特别说明,受体制备方法亦如文献方法,使用人胎盘膜。一般情况下,胰岛素受体结合实验使用0.025毫克胎盘膜。

[1570] 在胰岛素受体结合分析实验中,胰岛素标准的起始浓度和本发明融合蛋白的起始浓度均为100nM,然后将胰岛素和融合蛋白系列3倍稀释,分别得到7个不同浓度的溶液(100nM、33.33nM、11.11nM、3.70nM、1.23nM、0.41nM、0.13nM、0.04nM)。对于本发明中在胰岛素受体的活性低于人胰岛素标准10%的融合蛋白,蛋白起始浓度为500nM。

[1571] 截断的水溶性受体

[1572] 胰岛素受体、^{125}I-胰岛素(3pM)和系列3倍稀释的融合蛋白加入缓冲液[100mM Hepes,pH 8.0,100mM NaCl,10mM $MgCl_2$,0.5%(w/v)BSA,0.025%(w/v)Triton X-100],总体积200μL,在4℃培养48小时。受体及与受体结合的融合蛋白和配体用0.2%γ-球蛋白和500μL 25%(w/v)PEG 8000沉淀,测量沉淀中的放射性。受体的浓度要调节到在未添加融合蛋白的时候有15-20%的受体与配体结合。

[1573] 膜结合受体

[1574] 受体结合分析使用的膜结合受体来自高度表达全长胰岛素受体的BHK细胞。等量的转染BHK细胞(2000-5000)均匀分布在96孔板的每一孔,在包含10%(v/v)胎牛血清的Dulbecco's改良的Eagle's培养基(DMEM)中培养24小时后再进行受体结合分析。细胞先用结合缓冲液(DMEM,含0.50%BSA,20mM Hepes,pH 7.8)洗一遍,加入^{125}I-胰岛素(6.5pM)和溶于结合缓冲液的系列3倍稀释的融合蛋白。在16℃培养3小时,未结合的多肽用吸引器吸出,用1.2ml结合缓冲液洗一遍。细胞溶解于500μL 1%(w/v)SDS,100mM NaCl,25mM Hepes(pH 7.8),然后测量。细胞数量要调整到未加融合蛋白时有16-28%的受体与配体结合。

[1575] 胰岛素受体:^{125}I-胰岛素(30nCi)、系列3倍稀释的融合蛋白和胎盘膜(0.025mg)在0.05毫升上述缓冲液中,20℃培养1小时。样品用EHWP过滤器过滤,培养管和过滤器用2.5毫升不含牛白蛋白的冷缓冲液洗4遍。没有胎盘膜的情况下,少于5%的融合蛋白附着在过滤器上。对胎盘膜非特异结合可以通过添加过量的非碘化胰岛素(1μM)到培养混合物来测量。非特异结合通常占配体与胎盘膜结合总量的1%以下。

[1576] 特异结合百分比＝(结合放射量-非特异结合放射量/全部结合放射量-非特异结合放射量)x100。全部结合放射量是未添加融合蛋白时测得的放射总量。结合放射量是添加融合蛋白后测得的放射量。融合蛋白的IC_{50}使用Origin软件(OriginLab,Northampton,MA)计算。融合蛋白相对于人胰岛素标准的活性＝IC_{50}人胰岛素标准/IC_{50}融合蛋白。

[1577] 3.GLP-1cAMP分析

[1578] 表达人胰岛GLP-1受体的BHK(baby hamster kidney)细胞按文献准备(Knudsen和Pridal,1996,Eur.J.Pharm.318,429-435)。质膜按文献准备(Adelhorst等,1994,J.Biol.Chem.269,6275),在缓冲液(10mmol/l Tris-HCl、30mmol/l NaCl,pH 7.4、1mmol DTT、5mg/l亮抑酶肽、5mg/l抑肽素、100mg/l杆菌肽素、16mg/l抑蛋白酶肽)中均化,均匀混合物在一层41w/v％蔗糖上离心。两层之间的白色条带溶解在缓冲液中离心,质膜保存在-80℃。

[1579] 分析使用96孔微量滴定板,总体积140μl。缓冲液包含50mmol/l Tris-HCl,pH 7.4、1mmol/l EGTA、1.5mmol/l $MgSO_4$、1.7mmol/l ATP、20mM GTP、2mmol/l,3-异丁基-1-甲基黄嘌呤、0.01％吐温-20、0.1％人血清白蛋白。被测样品用缓冲液溶解和稀释,加到膜配制中。混合物在37°培养2小时。反应通过添加25μl 0.05mol/l HCl终止。样品稀释10倍后用亲近闪烁检测法(Scintillation Proximity Assay,SPA)测量cAMP。参考文献(Kahl等,“Scintillation Proximity Assay.”February,2005。DOI:10.1002/0471142301.ns0715s30。http://www.currentprotocols.com/WileyCDA/CPUnit/refId-ns0715.html)。

[1580] GLP-1(7-37)标准物的EC_{50}是61pM。

[1581] 4.GIP cAMP分析

[1582] 根据文献方法(Wheeler等,“Characterization of the carboxyl-terminal domain of the rat glucose-dependent insulinotropic polypeptide(GIP)receptor:a role for serines 426 and 427 in internalization”J.Biol.Chem.1999,274:24593-24601)。稳定表达GIP受体的CHO细胞转移到96孔微量滴定板,培养48小时。细胞用37℃的HEPES-缓冲的分析缓冲液液(DMEM/F12,15mM HEPES(Sigma-Aldrich),0.1％牛白蛋白(Sigma-Aldrich),pH 7.4)洗涤,预先培养60分钟。在细胞中加入样品(0.001～100nM融合蛋白,溶于10mM HEPES,pH 7.4、150mM NaCl、5mM KCl、2.5mM $CaCl_2$、1.2mM KH_2PO_4、1.2mM $MgSO_4$、25mM $NaHCO_3$、0.5mM 3-异丁基-1-甲基黄嘌呤和1％(w/v)牛白蛋白)培育30分钟。对于GIP受体拮抗剂,细胞先与培育15分钟,然后加入1nM GIP(1-42)培育30分钟。cAMP量用亲近闪烁检测法测量。

[1583] 5.GIP受体结合分析

[1584] GIP(5μg)以传统的氯胺-T方法碘化并用C-18柱纯化(Sep-Pak;Millipore Corp.),乙腈梯度是30-45％。放射性标记的GIP的比放射性强度(specific Activity)为10-50μCi/mg。^{125}I-GIP溶于分析缓冲液,浓度为3×10^5cpm/100μl。表达GIP受体的CHO细胞($1-5\times10^5$/孔)用结合缓冲液(DMEM/F12,20mm HEPES、0.1％牛白蛋白、0.5mg/ml杆菌肽素,pH7.4)洗两遍。加入^{125}I-GIP(50000cpm)和0.3-500nM融合蛋白,在4℃培养12-16小时。未与受体结合的^{125}I-GIP用真空分离。微量滴定板用冰冷的含有0.1％(w/v)牛白蛋白的PBS冲洗,在室温干燥。根据情况可以加入30μl Ultima Gold(Perkin-Elmer),用γ射线计数器测

量^{125}I-GIP含量。IC_{50}计算方法参见胰岛素受体结合分析。GIP(1-42)标准的IC_{50}是2.1±0.75nM。

[1585] 实验结果：

[1586] 通过对本发明的化合物进行GLP-1受体结合力、胰岛素受体结合力、GIP受体结合力和白介素-1受体结合力实验来检测这些化合物的生物活性，使用人GLP-1(7-37)作为GLP-1受体结合力的基准(100％)、人胰岛素作为胰岛素受体结合力的基准(100％)、GIP(1-42)作为GIP受体结合力的基准(100％)和野生型人IL-1Ra作为白介素-1受体拮抗蛋白的基准(100％)。得到的结果分别见表一、表二和表三。

[1587] 表一：GLP-1受体结合多肽与白介素-1受体拮抗蛋白的融合蛋白的生物活性

[1588]

编号	GLP-1受体(%)	Il-1ra受体(%)	编号	GLP-1受体(%)	Il-1ra受体(%)	编号	GLP-1受体(%)	Il-1ra受体(%)	编号	GLP-1受体(%)	Il-1ra受体(%)
G-1	52	33	G-22	60	47	G-43	41	40	G-64	70	34
G-2	53	40	G-23	27	24	G-44	40	40	G-65	77	36
G-3	61	46	G-24	32	27	G-45	46	42	G-66	76	35
G-4	67	45	G-25	33	29	G-46	45	43	G-67	52	35
G-5	45	37	G-26	26	30	G-47	42	41	G-68	51	33

[1589]

G-6	49	48	G-27	24	32	G-48	42	40	G-69	45	34
G-7	50	51	G-28	23	35	G-49	43	42	G-70	42	32
G-8	48	53	G-29	43	34	G-50	44	43	G-71	78	46
G-9	30	26	G-30	57	42	G-51	92	47	G-72	77	47
G-10	29	30	G-31	53	40	G-52	90	46	G-73	78	46
G-11	21	33	G-32	62	41	G-53	79	46	G-74	76	45
G-12	22	34	G-33	54	43	G-54	78	47	G-75	71	46
G-13	19	31	G-34	46	42	G-55	72	45	G-76	70	43
G-14	20	32	G-35	53	40	G-56	70	44	G-77	82	44
G-15	17	26	G-36	60	44	G-57	83	45	G-78	81	42
G-16	25	33	G-37	63	46	G-58	82	43	G-79	120	40
G-17	20	32	G-38	61	43	G-59	81	39	G-80	115	39
G-18	42	31	G-39	62	42	G-60	80	37	G-81	39	12
G-19	43	38	G-40	51	45	G-61	75	38	G-82	7	12
G-20	55	46	G-41	46	41	G-62	73	36	G-83	37	8
G-21	58	45	G-42	45	42	G-63	71	37	G-84	15	9

[1590] 表二：胰岛素受体结合多肽与白介素-1受体拮抗蛋白的融合蛋白的生物活性

[1591]

编号	胰岛素受体(%)	IL-1 受体(%)	编号	胰岛素受体(%)	IL-1 受体(%)	编号	胰岛素受体(%)	IL-1 受体(%)
IN-1	17	35	IN-25	19	38	IN-48	9	26
IN-2	17	34	IN-26	18	39	IN-49	27	25
IN-3	16	35	IN-27	10	31	IN-50	16	20
IN-4	20	39	IN-28	9	29	IN-51	49	37
IN-5	20	38	IN-29	53	45	IN-52	8	19
IN-6	18	37	IN-30	53	42	IN-53	47	36
IN-7	25	49	IN-31	9	33	IN-54	9	18
IN-8	25	47	IN-32	9	31	IN-55	38	35
IN-9	24	47	IN-33	16	40	IN-56	38	36
IN-10	26	50	IN-34	15	44	IN-57	20	23
IN-11	25	48	IN-35	19	45	IN-58	7	17
IN-12	25	48	IN-36	10	34	IN-59	21	19
IN-13	13	34	IN-37	14	30	IN-60	21	24
IN-14	12	32	IN-38	50	47	IN-61	23	22
IN-15	12	32	IN-39	14	33	IN-62	18	47
IN-16	18	42	IN-40	12	35	IN-63	17	45
IN-17	18	40	IN-41	47	46	IN-64	20	42

[1592]

IN-18	17	40	IN-42	13	31	IN-65	17	43
IN-19	23	47	IN-43	45	43	IN-66	15	41
IN-20	23	44	IN-44	11	32	IN-67	11	46
IN-21	21	43	IN-45	20	39	IN-68	5	10
IN-22	25	46	IN-46	10	28	IN-69	7	18
IN-23	25	46	IN-47	19	38	IN-70	8	42
IN-24	24	45						

[1593] 表三:GIP受体结合多肽与白介素-1受体拮抗蛋白的融合蛋白的生物活性

[1594]

编号	GIP受体(%)	IL-1受体(%)	编号	GIP受体(%)	IL-1受体(%)
GI-1	53	46	GI-16	(57)	43
GI-2	264	47	GI-17	(61)	47
GI-3	298	44	GI-18	(72)	46
GI-4	312	45	GI-19	(54)	50
GI-5	316	42	GI-20	(65)	48
GI-6	(50)	48	GI-21	(63)	45
GI-7	(53)	45	GI-22	36	21
GI-8	(55)	43	GI-23	(28)	19
GI-9	(55)	40	GI-24	137	50
GI-10	(6.2)	42	GI-25	24	18
GI-11	187	38	GI-26	(19)	23
GI-12	179	41	GI-27	42	67

GI-13	356	39	GI-28	79	51
GI-14	368	40	GI-29	156	24
GI-15	381	45	GI-30	(49)	58

[1595] 注:表中GI-1～GI-5、GI-11～GI-15、GI-22、GI-24、GI-25、GI-27～GI-29使用cAMP试验。其它蛋白使用GIP受体结合分析试验,在括号中表示的是蛋白在GIP受体结合分析试验中的活性与GIP(1-42)的比值。这些蛋白对GIP受体是抑制剂,因此使用受体结合试验而不是cAMP试验。

[1596] 动物试验

[1597] 1、对五周龄C57BL/6J小鼠喂食高脂肪/高蔗糖饲料(其中卡路里58%来自脂肪、26%来自碳水化合物、16%来自蛋白)。小鼠分为四组,每组6只。试验一组每日腹腔内注射生理盐水(0.9%w/v,NaCl),试验二组每日注射IL-1Ra(500nmol/kg),试验三组、四组每日注射融合蛋白G-2和G-20(50nmol/kg),连续12周,随后进行葡萄糖耐量试验。小鼠先禁食12小时,然后腹腔内注射葡萄糖(2mg/g),在0、15、30、60、90、120分钟采集血液,测量血糖。另外,在0和30分钟测量血清胰岛素水平。

[1598] 在图7所示试验中,IL-Ra组与生理盐水组相比,显示出更好的控制血糖的效果。而G-2和G-20组的小鼠的糖耐量明显增强,不仅血糖高峰低,而且血糖下降速度快。在12周治疗过程中,G-2和G-20的用量仅为IL-1Ra的1/10,表明GLP-1受体结合多肽与白介素-1受体拮抗蛋白的融合蛋白在体内生物活性和治疗效果都显著优于IL-1Ra。

[1599] 在图8所示试验中,IL-Ra组的空腹血清胰岛素水平明显低于生理盐水组。生理盐水组在糖耐量试验过程中胰岛素水平变化很小,而IL-1Ra组的胰岛素水平是空腹时的2倍。G-2和G-20组的空腹血清胰岛素水平最低,而在糖耐量试验过程中胰岛素水平达到空腹时的2.5-4倍,显示G-2和G-20对胰岛功能的调节、保护作用优于单独使用IL-1Ra。显示出更好的控制血糖的效果。

[1600] 2、对五周龄C57BL/6J小鼠喂食高脂肪/高蔗糖饲料(其中卡路里58%来自脂肪、26%来自碳水化合物、16%来自蛋白)。小鼠分为四组,每组6只。试验一组(对照组)每日腹腔内注射生理盐水(0.9%w/v,NaCl),试验二组每日注射IL-1Ra(500nmol/kg),试验三组、四组每日餐后注射融合蛋白IN-7和IN-62(30nmol/kg),连续12周,随后进行胰岛素耐量试验。小鼠先禁食5小时,然后腹腔内注射人胰岛素(0.75U/kg),在0、15、30、60、90、120分钟采集血液,测量血糖。

[1601] 高脂肪食物往往导致高胰岛素血症,造成对胰岛素的敏感性下降,这是很大一部分肥胖的2型糖尿病患者的发病原因。提高胰岛素敏感性是预防甚至治疗糖尿病的重要方法之一。在图9所示试验中,IL-Ra组与生理盐水组相比,显示出较好的胰岛素敏感性。GI-3和GI-7组的小鼠的胰岛素敏感性更优异。在12周治疗过程中,IN-7和IN-62的用量仅为IL-1Ra的1/17,表明胰岛素与白介素-1受体拮抗蛋白的融合蛋白在体内生物活性和治疗效果都显著优于IL-1Ra。

[1602] 3、对五周龄C57BL/6J小鼠喂食高脂肪/高蔗糖饲料(其中卡路里58%来自脂肪、26%来自碳水化合物、16%来自蛋白)。小鼠分为四组,每组6只。试验一组(对照组)每日腹腔内注射生理盐水(0.9%w/v,NaCl),试验二组每日注射IL-1Ra(500nmol/kg),试验三组、四组每日注射融合蛋白GI-3和GI-7(50nmol/kg),连续12周,随后进行葡萄糖耐量试验。小

鼠先禁食12小时，然后腹腔内注射葡萄糖(2mg/g)，在0、15、30、60分钟采集血液，测量血糖。

[1603] 在图10所示试验中，IL-Ra组与对照生理盐水组相比，显示出更好的控制血糖的效果。而GI-3和GI-7组的小鼠的糖耐量明显增强，血糖高峰低。在12周治疗过程中，G-2和G-20的用量仅为IL-1Ra的1/10，表明GIP受体结合多肽与白介素-1受体拮抗蛋白的融合蛋白在体内生物活性和治疗效果都显著优于IL-1Ra。

[1604] 上述试验中的融合蛋白在各自相应的受体测试中(表一、二、三)并不一定优于标准蛋白(IL-1Ra、GLP(7-37)、人胰岛素、GIP(1-42))，但融合蛋白通过其组成的两种蛋白/多肽的协同作用，在体内表现出更优异的生物活性和治疗效果，证明了融合蛋白的设计和制备方法的正确性。本发明中的融合蛋白有希望作为一类新型化合物应用于糖尿病的预防与治疗。

序列表

<110> 爱德迪安(北京)生物技术有限公司

<120> 用于糖尿病治疗的蛋白、蛋白缀合物及其应用

<130> DSP1F171607ZX-DIV1

<150> CN 201210157196.6

<151> 2012-05-18

<160> 203

<170> PatentIn version 3.5

<210> 1

<211> 191

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 G-1

<400> 1

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30
Ser Gly Ala Pro Pro Pro Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys
        35                  40                  45
Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu
    50                  55                  60
Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn
65                  70                  75                  80
Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe
                85                  90                  95
Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly
            100                 105                 110
Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser
        115                 120                 125
Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser
    130                 135                 140
Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu
145                 150                 155                 160
Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro
                165                 170                 175
Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
```

180 185 190

<210> 2
<211> 196
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-2
<400> 2

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly
35 40 45
Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln
50 55 60
Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln
65 70 75 80
Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu
85 90 95
Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser
100 105 110
Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn
115 120 125
Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe
130 135 140
Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys
145 150 155 160
Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser
165 170 175
Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe
180 185 190
Gln Glu Asp Glu
195

<210> 3
<211> 201
<212> PRT
<213> 人工序列
<220>

<223> 融合蛋白 G-3

<400> 3

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
50 55 60
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
85 90 95
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
100 105 110
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
115 120 125
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
130 135 140
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
145 150 155 160
Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
165 170 175
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
180 185 190
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 4

<211> 206

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 G-4

<400> 4

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met
50 55 60
Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg
65 70 75 80
Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu
85 90 95
Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu
100 105 110
Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp
115 120 125
Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu
130 135 140
Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly
145 150 155 160
Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys
165 170 175
Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp
180 185 190
Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200 205

<210> 5
<211> 182
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-5
<400> 5

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Arg Pro
20 25 30
Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val
35 40 45
Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr
50 55 60
Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro
65 70 75 80

Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys
85 90 95
Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala
100 105 110
Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe
115 120 125
Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala
130 135 140
Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro
145 150 155 160
Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe
165 170 175
Tyr Phe Gln Glu Asp Glu
180

<210> 6
<211> 185
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-6
<400> 6
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Gly Gly
20 25 30
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
35 40 45
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
50 55 60
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
65 70 75 80
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
85 90 95
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
100 105 110
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
115 120 125
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
130 135 140

Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
145 150 155 160
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
165 170 175
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
180 185

<210> 7
<211> 190
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-7
<400> 7
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Gly Gly
20 25 30
Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met
35 40 45
Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg
50 55 60
Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu
65 70 75 80
Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu
85 90 95
Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp
100 105 110
Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu
115 120 125
Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly
130 135 140
Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys
145 150 155 160
Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp
165 170 175
Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
180 185 190

<210> 8
<211> 195

<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-8
<400> 8

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Gly Gly
            20                  25                  30
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg
        35                  40                  45
Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys
    50                  55                  60
Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly
65                  70                  75                  80
Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro
                85                  90                  95
His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys
            100                 105                 110
Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile
        115                 120                 125
Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile
    130                 135                 140
Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro
145                 150                 155                 160
Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu
                165                 170                 175
Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln
            180                 185                 190
Glu Asp Glu
        195
```

<210> 9
<211> 196
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-9
<220>
<221> MOD_RES

<222> (160)..(160)
<223> S-马来酰亚胺-(CH2)4-NH- (Nα- (HOOC(CH2)14
CO)-γ-Glu),S是半胱氨酸侧链的硫原子
<400> 9

His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Met	Glu	Glu
1				5				10						15	
Glu	Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser
			20					25					30		
Ser	Gly	Ala	Pro	Pro	Pro	Ser	Gly	Gly	Gly	Gly	Ser	Arg	Pro	Ser	Gly
		35					40					45			
Arg	Lys	Ser	Ser	Lys	Met	Gln	Ala	Phe	Arg	Ile	Trp	Asp	Val	Asn	Gln
	50					55					60				
Lys	Thr	Phe	Tyr	Leu	Arg	Asn	Asn	Gln	Leu	Val	Ala	Gly	Tyr	Leu	Gln
65				70					75					80	
Gly	Pro	Asn	Val	Asn	Leu	Glu	Glu	Lys	Ile	Asp	Val	Val	Pro	Ile	Glu
				85					90					95	
Pro	His	Ala	Leu	Phe	Leu	Gly	Ile	His	Gly	Gly	Lys	Met	Cys	Leu	Ser
			100					105					110		
Cys	Val	Lys	Ser	Gly	Asp	Glu	Thr	Arg	Leu	Gln	Leu	Glu	Ala	Val	Asn
		115					120					125			
Ile	Thr	Asp	Leu	Ser	Glu	Asn	Arg	Lys	Gln	Asp	Lys	Arg	Phe	Ala	Phe
	130					135					140				
Ile	Arg	Ser	Asp	Ser	Gly	Pro	Thr	Thr	Ser	Phe	Glu	Ser	Ala	Ala	Cys
145				150					155					160	
Pro	Gly	Trp	Phe	Leu	Cys	Thr	Ala	Met	Glu	Ala	Asp	Gln	Pro	Val	Ser
				165					170					175	
Leu	Thr	Asn	Met	Pro	Asp	Glu	Gly	Val	Met	Val	Thr	Lys	Phe	Tyr	Phe
			180					185					190		
Gln	Glu	Asp	Glu												
		195													

<210> 10
<211> 196
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-10
<220>
<221> MOD_RES
<222> (128)..(128)

<223> S-CH2-CONH-PEG20K,S是半胱氨酸侧链的硫原子
<400> 10

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly
35 40 45
Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln
50 55 60
Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln
65 70 75 80
Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu
85 90 95
Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser
100 105 110
Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Cys
115 120 125
Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe
130 135 140
Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Ser
145 150 155 160
Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser
165 170 175
Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe
180 185 190
Gln Glu Asp Glu
195

<210> 11
<211> 191
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-11
<220>
<221> MOD_RES
<222> (155)..(155)
<223> S-CH2-CONH-PEG20K,S是半胱氨酸侧链的硫原子
<400> 11

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Gly Gly
20 25 30
Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys
35 40 45
Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu
50 55 60
Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn
65 70 75 80
Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe
85 90 95
Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly
100 105 110
Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser
115 120 125
Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser
130 135 140
Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu
145 150 155 160
Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro
165 170 175
Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
180 185 190

<210> 12
<211> 201
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-12
<220>
<221> MOD_RES
<222> (133)..(133)
<223> S-马来酰亚胺-(CH2)4-NH-(Nα-(HOOC(CH2)14CO)-γ-Glu),S是半胱氨酸侧链的硫原子
<400> 12
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser

20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
50 55 60
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
85 90 95
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
100 105 110
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
115 120 125
Leu Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
130 135 140
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
145 150 155 160
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
165 170 175
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
180 185 190
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 13
<211> 185
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-13
<220>
<221> MOD_RES
<222> (149)..(149)
<223> S-马来酰亚胺-PEG20K,S是半胱氨酸侧链的硫原子
<400> 13
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Gly Gly
20 25 30
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile

35 40 45

Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
50 55 60

Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
65 70 75 80

Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
85 90 95

Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
100 105 110

Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
115 120 125

Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
130 135 140

Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
145 150 155 160

Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
165 170 175

Thr Lys Phe Tyr Phe Gln Glu Asp Glu
180 185

<210> 14

<211> 185

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 G-14

<220>

<221> MOD_RES

<222> (117)..(117)

<223> S-马来酰亚胺-(CH2)4-NH-(Nα-(HOOC(CH2)14 CO)-γ-Glu),S是半胱氨酸侧链的硫原子

<400> 14

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Gly Gly
20 25 30

Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
35 40 45

Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
50 55 60

Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
65 70 75 80
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
85 90 95
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
100 105 110
Leu Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
115 120 125
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
130 135 140
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
145 150 155 160
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
165 170 175
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
180 185

<210> 15
<211> 201
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-15
<220>
<221> MOD_RES
<222> (27)..(27)
<223> S-马来酰亚胺-(CH2)4-NH- (Nα-(HOOC(CH2)14 CO)
-γ-Glu),S是半胱氨酸侧链的硫原子
<400> 15
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Cys Asn Gly Gly Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
50 55 60
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp

85 90 95
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
100 105 110
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
115 120 125
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
130 135 140
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
145 150 155 160
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
165 170 175
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
180 185 190
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 16
<211> 201
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-16
<220>
<221> MOD_RES
<222> (39)..(39)
<223> S-CH2-CONH-PEG20K,S是半胱氨酸侧链的硫原子
<400> 16
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
50 55 60
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
85 90 95
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly

100 105 110
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
115 120 125
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
130 135 140
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
145 150 155 160
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
165 170 175
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
180 185 190
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 17
<211> 201
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-17
<220>
<221> MOD_RES
<222> (20)..(20)
<223> S-马来酰亚胺-(CH2)4-NH-(Nα-(HOOC(CH2)14CO)-γ-Glu),S是半胱氨酸侧链的硫原子
<400> 17
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Cys Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
50 55 60
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
85 90 95
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
100 105 110

Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
115 120 125
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
130 135 140
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
145 150 155 160
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
165 170 175
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
180 185 190
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 18
<211> 183
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-18
<400> 18

His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Arg
20 25 30
Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp
35 40 45
Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly
50 55 60
Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val
65 70 75 80
Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met
85 90 95
Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu
100 105 110
Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg
115 120 125
Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser
130 135 140
Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln
145 150 155 160

Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys
165 170 175
Phe Tyr Phe Gln Glu Asp Glu
180

<210> 19
<211> 187
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-19
<400> 19

His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Gly
20 25 30
Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe
35 40 45
Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln
50 55 60
Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys
65 70 75 80
Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His
85 90 95
Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg
100 105 110
Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys
115 120 125
Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr
130 135 140
Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met
145 150 155 160
Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val
165 170 175
Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
180 185

<210> 20
<211> 192
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白 G-20
<400> 20

His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Gly
20 25 30
Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser
35 40 45
Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr
50 55 60
Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val
65 70 75 80
Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu
85 90 95
Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser
100 105 110
Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu
115 120 125
Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp
130 135 140
Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe
145 150 155 160
Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met
165 170 175
Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
180 185 190

<210> 21
<211> 197
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-21
<400> 21

His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Gly
20 25 30
Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser

35 40 45

Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn
50 55 60
Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu
65 70 75 80
Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile
85 90 95
Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu
100 105 110
Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val
115 120 125
Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala
130 135 140
Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala
145 150 155 160
Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val
165 170 175
Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr
180 185 190
Phe Gln Glu Asp Glu
195

<210> 22
<211> 201
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-22
<400> 22

His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
50 55 60
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp

85 90 95
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
100 105 110
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
115 120 125
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
130 135 140
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
145 150 155 160
Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
165 170 175
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
180 185 190
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 23
<211> 183
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-23
<220>
<221> MOD_RES
<222> (147)..(147)
<223> S-CH2-CONH-PEG20K,S是半胱氨酸侧链的硫原子
<400> 23
His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Arg
20 25 30
Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp
35 40 45
Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly
50 55 60
Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val
65 70 75 80
Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met
85 90 95
Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu

100 105 110
Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg
115 120 125
Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser
130 135 140
Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln
145 150 155 160
Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys
165 170 175
Phe Tyr Phe Gln Glu Asp Glu
180

<210> 24
<211> 187
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-24
<220>
<221> MOD_RES
<222> (151)..(151)
<223> S-CH2-CONH-PEG20K,S是半胱氨酸侧链的硫原子
<400> 24
His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Gly
20 25 30
Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe
35 40 45
Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln
50 55 60
Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys
65 70 75 80
Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His
85 90 95
Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg
100 105 110
Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys
115 120 125
Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr

130 135 140

Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met
145 150 155 160

Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val
165 170 175

Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
180 185

<210> 25

<211> 187

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 G-25

<220>

<221> MOD_RES

<222> (119)..(119)

<223> S-马来酰亚胺-(CH2)4-NH- (Nα-(HOOC(CH2)14 CO)-γ-Glu),S是半胱氨酸侧链的硫原子

<400> 25

His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1 5 10 15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Gly
20 25 30

Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe
35 40 45

Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln
50 55 60

Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys
65 70 75 80

Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His
85 90 95

Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg
100 105 110

Leu Gln Leu Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys
115 120 125

Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr
130 135 140

Ser Phe Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met
145 150 155 160

Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val
165 170 175
Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
180 185

<210> 26
<211> 192
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-26
<220>
<221> MOD_RES
<222> (156)..(156)
<223> S-CH2-CONH-PEG2OK,S是半胱氨酸侧链的硫原子
<400> 26

His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Gly
20 25 30
Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser
35 40 45
Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr
50 55 60
Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val
65 70 75 80
Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu
85 90 95
Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser
100 105 110
Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu
115 120 125
Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp
130 135 140
Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe
145 150 155 160
Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met
165 170 175
Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
180 185 190

<210> 27
<211> 192
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-27
<220>
<221> MOD_RES
<222> (124)..(124)
<223> S-马来酰亚胺-(CH2)4-NH-(Nα-(HOOC(CH2)14
CO)-γ-Glu),S是半胱氨酸侧链的硫原子
<400> 27

His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu	Glu	Glu
1				5				10						15	
Gln	Ala	Ala	Lys	Glu	Phe	Ile	Ala	Trp	Leu	Val	Lys	Gly	Arg	Gly	Gly
			20					25					30		
Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Arg	Pro	Ser	Gly	Arg	Lys	Ser	Ser
		35					40					45			
Lys	Met	Gln	Ala	Phe	Arg	Ile	Trp	Asp	Val	Asn	Gln	Lys	Thr	Phe	Tyr
	50					55					60				
Leu	Arg	Asn	Asn	Gln	Leu	Val	Ala	Gly	Tyr	Leu	Gln	Gly	Pro	Asn	Val
65					70					75					80
Asn	Leu	Glu	Glu	Lys	Ile	Asp	Val	Val	Pro	Ile	Glu	Pro	His	Ala	Leu
				85					90					95	
Phe	Leu	Gly	Ile	His	Gly	Gly	Lys	Met	Cys	Leu	Ser	Cys	Val	Lys	Ser
			100					105					110		
Gly	Asp	Glu	Thr	Arg	Leu	Gln	Leu	Glu	Ala	Val	Cys	Ile	Thr	Asp	Leu
		115					120					125			
Ser	Glu	Asn	Arg	Lys	Gln	Asp	Lys	Arg	Phe	Ala	Phe	Ile	Arg	Ser	Asp
	130					135					140				
Ser	Gly	Pro	Thr	Thr	Ser	Phe	Glu	Ser	Ala	Ala	Ser	Pro	Gly	Trp	Phe
145					150					155					160
Leu	Cys	Thr	Ala	Met	Glu	Ala	Asp	Gln	Pro	Val	Ser	Leu	Thr	Asn	Met
				165					170					175	
Pro	Asp	Glu	Gly	Val	Met	Val	Thr	Lys	Phe	Tyr	Phe	Gln	Glu	Asp	Glu
			180					185					190		

<210> 28
<211> 197
<212> PRT

<213> 人工序列
<220>
<223> 融合蛋白 G-28
<220>
<221> MOD_RES
<222> (161)..(161)
<223> S-CH2-CONH-PEG20K,S是半胱氨酸侧链的硫原子
<400> 28

```
His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1               5                  10                  15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Gly
            20                  25                  30
Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser
        35                  40                  45
Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn
    50                  55                  60
Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu
65                  70                  75                  80
Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile
                85                  90                  95
Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu
            100                 105                 110
Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val
        115                 120                 125
Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala
    130                 135                 140
Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala
145                 150                 155                 160
Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val
                165                 170                 175
Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr
            180                 185                 190
Phe Gln Glu Asp Glu
        195
```

<210> 29
<211> 201
<212> PRT
<213> 人工序列
<220>

<223> 融合蛋白 G-29
<220>
<221> MOD_RES
<222> (165)..(165)
<223> S-马来酰亚胺-(CH2)4-NH-(Nα-(HOOC(CH2)14CO)-γ-Glu),S是半胱氨酸侧链的硫原子
<400> 29

His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu	Glu	Glu
1				5				10					15		
Gln	Ala	Ala	Lys	Glu	Phe	Ile	Ala	Trp	Leu	Val	Lys	Gly	Arg	Pro	Ser
			20					25				30			
Ser	Gly	Ala	Pro	Pro	Pro	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly
		35					40					45			
Ser	Arg	Pro	Ser	Gly	Arg	Lys	Ser	Ser	Lys	Met	Gln	Ala	Phe	Arg	Ile
	50					55					60				
Trp	Asp	Val	Asn	Gln	Lys	Thr	Phe	Tyr	Leu	Arg	Asn	Asn	Gln	Leu	Val
65					70					75					80
Ala	Gly	Tyr	Leu	Gln	Gly	Pro	Asn	Val	Asn	Leu	Glu	Glu	Lys	Ile	Asp
				85					90					95	
Val	Val	Pro	Ile	Glu	Pro	His	Ala	Leu	Phe	Leu	Gly	Ile	His	Gly	Gly
			100					105					110		
Lys	Met	Cys	Leu	Ser	Cys	Val	Lys	Ser	Gly	Asp	Glu	Thr	Arg	Leu	Gln
		115					120					125			
Leu	Glu	Ala	Val	Asn	Ile	Thr	Asp	Leu	Ser	Glu	Asn	Arg	Lys	Gln	Asp
	130					135					140				
Lys	Arg	Phe	Ala	Phe	Ile	Arg	Ser	Asp	Ser	Gly	Pro	Thr	Thr	Ser	Phe
145					150					155					160
Glu	Ser	Ala	Ala	Cys	Pro	Gly	Trp	Phe	Leu	Cys	Thr	Ala	Met	Glu	Ala
				165					170					175	
Asp	Gln	Pro	Val	Ser	Leu	Thr	Asn	Met	Pro	Asp	Glu	Gly	Val	Met	Val
			180					185					190		
Thr	Lys	Phe	Tyr	Phe	Gln	Glu	Asp	Glu							
		195					200								

<210> 30
<211> 201
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-30

<220>
<221> MOD_RES
<222> (39)..(39)
<223> S-马来酰亚胺-(CH2)15-COOH,S是半胱氨酸侧链的硫原子
<400> 30

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
50 55 60
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
85 90 95
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
100 105 110
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
115 120 125
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
130 135 140
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
145 150 155 160
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
165 170 175
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
180 185 190
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 31
<211> 201
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-31
<220>
<221> MOD_RES

<222> (39)..(39)
<223> S-马来酰亚胺-(CH2)17-COOH,S是半胱氨酸侧链的硫原子
<400> 31

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
50 55 60
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
85 90 95
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
100 105 110
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
115 120 125
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
130 135 140
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
145 150 155 160
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
165 170 175
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
180 185 190
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 32
<211> 201
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-32
<220>
<221> MOD_RES
<222> (39)..(39)
<223> S-CH2-CONH-(CH2CH2O)2-(CH2)2-NH-(Nα-(HOOC(CH2)14CO)-γ-Glu),S是半

胱氨酸侧链的硫原子

<400> 32

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
50 55 60
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
85 90 95
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
100 105 110
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
115 120 125
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
130 135 140
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
145 150 155 160
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
165 170 175
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
180 185 190
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 33

<211> 201

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 G-33

<220>

<221> MOD_RES

<222> (27)..(27)

<223> S-CH2-CONH-(CH2CH2O)2-(CH2)2-NH-(Nα-(HOOC(CH2)14CO)-γ-Glu),S是半胱氨酸侧链的硫原子

<400> 33

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Cys Asn Gly Gly Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
50 55 60
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
85 90 95
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
100 105 110
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
115 120 125
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
130 135 140
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
145 150 155 160
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
165 170 175
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
180 185 190
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 34

<211> 201

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 G-34

<220>

<221> MOD_RES

<222> (20)..(20)

<223> S-CH2-CONH-(CH2CH2O)2-(CH2)2-NH-(Nα-(HOOC(CH2)14CO)-γ-Glu),S是半胱氨酸侧链的硫原子

<400> 34

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Cys Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
50 55 60
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
85 90 95
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
100 105 110
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
115 120 125
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
130 135 140
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
145 150 155 160
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
165 170 175
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
180 185 190
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 35
<211> 201
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-35
<220>
<221> MOD_RES
<222> (32)..(32)
<223> S-CH2-CONH-(CH2CH2O)2-(CH2)2-NH-(Nα-(HOOC(CH2)14CO)-γ-Glu),S是半胱氨酸侧链的硫原子
<400> 35
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu

1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Cys
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
50 55 60
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
85 90 95
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
100 105 110
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
115 120 125
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
130 135 140
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
145 150 155 160
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
165 170 175
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
180 185 190
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 36
<211> 201
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-36
<220>
<221> MOD_RES
<222> (133)..(133)
<223> S-马来酰亚胺-(CH2)15-COOH,S是半胱氨酸侧链的硫原子
<400> 36
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser

20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
50 55 60
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
85 90 95
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
100 105 110
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
115 120 125
Leu Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
130 135 140
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
145 150 155 160
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
165 170 175
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
180 185 190
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 37
<211> 201
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-37
<220>
<221> MOD_RES
<222> (133)..(133)
<223> S-CH2-CONH-(CH2CH2O)2-(CH2)2-NH-(Nα-(HOOC(CH2)14CO)-γ-Glu),S是半胱氨酸侧链的硫原子
<400> 37
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
50 55 60
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
85 90 95
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
100 105 110
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
115 120 125
Leu Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
130 135 140
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
145 150 155 160
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
165 170 175
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
180 185 190
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 38
<211> 201
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-38
<220>
<221> MOD_RES
<222> (165)..(165)
<400> 38
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile

50 55 60

Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80

Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
85 90 95

Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
100 105 110

Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
115 120 125

Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
130 135 140

Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
145 150 155 160

Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
165 170 175

Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
180 185 190

Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 39

<211> 201

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 G-39

<220>

<221> MOD_RES

<222> (165)..(165)

<223> S-CH2-CONH-(CH2CH2O)4-(CH2)2-NH-(Nα-(HOOC(CH2)16CO)-γ-Glu),S是半胱氨酸侧链的硫原子

<400> 39

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45

Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
50 55 60

Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
85 90 95
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
100 105 110
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
115 120 125
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
130 135 140
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
145 150 155 160
Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
165 170 175
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
180 185 190
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 40
<211> 193
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-40
<220>
<221> MOD_RES
<222> (31)..(31)
<223> S-马来酰亚胺-(CH2)15-COOH,S是半胱氨酸侧链的硫原子
<400> 40
His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Cys Gly
20 25 30
Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser
35 40 45
Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe
50 55 60
Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn
65 70 75 80

Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala
85 90 95
Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys
100 105 110
Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp
115 120 125
Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser
130 135 140
Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly Trp
145 150 155 160
Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn
165 170 175
Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp
180 185 190
Glu

<210> 41
<211> 193
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-41
<220>
<221> MOD_RES
<222> (31)..(31)
<223> S-CH2-CONH-(CH2CH2O)2-(CH2)2-NH-(Nα-(HOOC(CH2)14CO)-γ-Glu),S是半胱氨酸侧链的硫原子
<400> 41
His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Cys Gly
20 25 30
Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser
35 40 45
Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe
50 55 60
Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn
65 70 75 80
Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala
85 90 95

Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys
100 105 110
Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp
115 120 125
Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser
130 135 140
Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly Trp
145 150 155 160
Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn
165 170 175
Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp
180 185 190
Glu

<210> 42
<211> 192
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-42
<220>
<221> MOD_RES
<222> (124)..(124)
<223> S-马来酰亚胺-(CH2)17-COOH,S是半胱氨酸侧链的硫原子
<400> 42
His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Gly
20 25 30
Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser
35 40 45
Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr
50 55 60
Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val
65 70 75 80
Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu
85 90 95
Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser
100 105 110
Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Cys Ile Thr Asp Leu

115 120 125
Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp
130 135 140
Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly Trp Phe
145 150 155 160
Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met
165 170 175
Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
180 185 190

<210> 43
<211> 192
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-43
<220>
<221> MOD_RES
<222> (20)..(20)
<223> S-CH2-CONH-(CH2CH2O)2-(CH2)2-NH-(Nα-(HOOC(CH2)14CO)-γ-Glu),S是半胱氨酸侧链的硫原子
<400> 43
His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1 5 10 15
Gln Ala Ala Cys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Gly
20 25 30
Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser
35 40 45
Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr
50 55 60
Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val
65 70 75 80
Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu
85 90 95
Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser
100 105 110
Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu
115 120 125
Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp
130 135 140

Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly Trp Phe
145 150 155 160
Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met
165 170 175
Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
180 185 190

<210> 44
<211> 192
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-44
<220>
<221> MOD_RES
<222> (20)..(20)
<223> S-CH2-CONH-(CH2CH2O)2-(CH2)2-NH-(Nα-(HOOC(CH2)14CO)-γ-Glu),S是半胱氨酸侧链的硫原子
<400> 44
His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
1 5 10 15
Gln Ala Ala Cys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Gly
20 25 30
Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser
35 40 45
Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr
50 55 60
Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val
65 70 75 80
Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu
85 90 95
Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser
100 105 110
Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu
115 120 125
Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp
130 135 140
Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly Trp Phe
145 150 155 160
Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met

165 170 175
Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
180 185 190

<210> 45
<211> 192
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-45
<220>
<221> MOD_RES
<222> (10)..(10)
<223> S-CH2-CONH-(CH2CH2O)2-(CH2)2-NH-(Nα-(HOOC(CH2)14CO-γ-Glu-N-γ-Glu),S是半胱氨酸侧链的硫原子
<400> 45
His Gly Glu Gly Thr Phe Thr Ser Asp Cys Ser Ser Tyr Leu Glu Glu
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Gly
20 25 30
Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser
35 40 45
Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr
50 55 60
Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val
65 70 75 80
Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu
85 90 95
Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser
100 105 110
Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu
115 120 125
Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp
130 135 140
Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly Trp Phe
145 150 155 160
Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met
165 170 175
Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
180 185 190

<210> 46
<211> 192
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-46
<220>
<221> MOD_RES
<222> (10)..(10)
<223> S-CH2-CONH-(CH2CH2O)2-(CH2)2-NH-(Nα-(HOOC(CH2)14CO)-γ-Glu),S是半胱氨酸侧链的硫原子
<400> 46

His Ala Glu Gly Thr Phe Thr Ser Asp Cys Ser Ser Tyr Leu Glu Gly
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Gly
20 25 30
Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser
35 40 45
Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr
50 55 60
Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val
65 70 75 80
Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu
85 90 95
Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser
100 105 110
Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu
115 120 125
Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp
130 135 140
Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly Trp Phe
145 150 155 160
Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met
165 170 175
Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
180 185 190

<210> 47
<211> 192
<212> PRT

<213> 人工序列
<220>
<223> 融合蛋白 G-47
<220>
<221> MOD_RES
<222> (28)..(28)
<223> S-CH2-CONH-(CH2CH2O)2-(CH2)2-NH-(Nα-(HOOC(CH2)14CO)-γ-Glu),S是半胱氨酸侧链的硫原子
<400> 47

```
His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1               5                  10                  15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Cys Gly Arg Gly Gly
            20                  25                  30
Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser
        35                  40                  45
Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr
    50                  55                  60
Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val
65                  70                  75                  80
Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu
                85                  90                  95
Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser
            100                 105                 110
Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu
        115                 120                 125
Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp
    130                 135                 140
Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly Trp Phe
145                 150                 155                 160
Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met
                165                 170                 175
Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
            180                 185                 190
```

<210> 48
<211> 192
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-48

<220>
<221> MOD_RES
<222> (124)..(124)
<223> S-CH2-CONH-(CH2CH2O)4-(CH2)2-NH-(Nα-(HOOC(CH2)16CO)-γ-Glu),S是半胱氨酸侧链的硫原子
<400> 48

His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu	Glu	Glu
1				5				10						15	
Gln	Ala	Ala	Lys	Glu	Phe	Ile	Ala	Trp	Leu	Val	Lys	Gly	Arg	Gly	Gly
			20					25					30		
Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Arg	Pro	Ser	Gly	Arg	Lys	Ser	Ser
		35					40					45			
Lys	Met	Gln	Ala	Phe	Arg	Ile	Trp	Asp	Val	Asn	Gln	Lys	Thr	Phe	Tyr
	50					55					60				
Leu	Arg	Asn	Asn	Gln	Leu	Val	Ala	Gly	Tyr	Leu	Gln	Gly	Pro	Asn	Val
65					70					75					80
Asn	Leu	Glu	Glu	Lys	Ile	Asp	Val	Val	Pro	Ile	Glu	Pro	His	Ala	Leu
				85					90					95	
Phe	Leu	Gly	Ile	His	Gly	Gly	Lys	Met	Cys	Leu	Ser	Cys	Val	Lys	Ser
			100					105					110		
Gly	Asp	Glu	Thr	Arg	Leu	Gln	Leu	Glu	Ala	Val	Cys	Ile	Thr	Asp	Leu
		115					120					125			
Ser	Glu	Asn	Arg	Lys	Gln	Asp	Lys	Arg	Phe	Ala	Phe	Ile	Arg	Ser	Asp
	130					135					140				
Ser	Gly	Pro	Thr	Thr	Ser	Phe	Glu	Ser	Ala	Ala	Ser	Pro	Gly	Trp	Phe
145					150					155					160
Leu	Cys	Thr	Ala	Met	Glu	Ala	Asp	Gln	Pro	Val	Ser	Leu	Thr	Asn	Met
				165					170					175	
Pro	Asp	Glu	Gly	Val	Met	Val	Thr	Lys	Phe	Tyr	Phe	Gln	Glu	Asp	Glu
			180					185					190		

<210> 49
<211> 192
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-49
<220>
<221> MOD_RES
<222> (156)..(156)

<223> S-马来酰亚胺-(CH2)15-COOH,S是半胱氨酸侧链的硫原子

<400> 49

His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Gly
20 25 30
Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser
35 40 45
Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr
50 55 60
Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val
65 70 75 80
Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu
85 90 95
Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser
100 105 110
Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu
115 120 125
Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp
130 135 140
Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe
145 150 155 160
Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met
165 170 175
Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
180 185 190

<210> 50

<211> 192

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 G-50

<220>

<221> MOD_RES

<222> (156)..(156)

<223> S-CH2-CONH-(CH2CH2O)2-(CH2)2-NH-(Nα-(HOOC(CH2)14CO)-γ-Glu),S是半胱氨酸侧链的硫原子

<400> 50

His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu

1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Gly
20 25 30
Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser
35 40 45
Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr
50 55 60
Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val
65 70 75 80
Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu
85 90 95
Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser
100 105 110
Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu
115 120 125
Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp
130 135 140
Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe
145 150 155 160
Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met
165 170 175
Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
180 185 190

<210> 51
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-51
<220>
<221> MOD_RES
<222> (84)..(84)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是 SEQ ID NO:185,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;
<400> 51
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15

Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 52
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-52
<220>
<221> MOD_RES
<222> (116)..(116)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:185,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白
<400> 52
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys

50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 53
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-53
<220>
<221> MOD_RES
<222> (84)..(84)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,,其中GLP-1受体结合多肽的序列是:SEQ ID NO:186,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白
<400> 53
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95

Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 54
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-54
<220>
<221> MOD_RES
<222> (116)..(116)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:186,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白
<400> 54
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr

130 135 140

Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 55
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-55
<220>
<221> MOD_RES
<222> (84)..(84)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是:SEQ ID NO:187,通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白
<400> 55

Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 56
<211> 152

<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-56
<220>
<221> MOD_RES
<222> (116)..(116)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:187,通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白

<400> 56

```
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1               5                  10                  15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
            20                  25                  30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
        35                  40                  45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
    50                  55                  60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65                  70                  75                  80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
                85                  90                  95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
            100                 105                 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
        115                 120                 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
    130                 135                 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145                 150
```

<210> 57
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-57
<220>

<221> MOD_RES
<222> (84)..(84)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是:SEQ ID NO:188,通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白
<400> 57

```
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1               5                  10                  15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
            20                  25                  30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
        35                  40                  45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
    50                  55                  60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65                  70                  75                  80
Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
                85                  90                  95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
            100                 105                 110
Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
        115                 120                 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
    130                 135                 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145                 150
```

<210> 58
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-58
<220>
<221> MOD_RES
<222> (116)..(116)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:188,通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗

蛋白

<400> 58

Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 59

<211> 152

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 G-59

<220>

<221> MOD_RES

<222> (84)..(84)

<223> S-马来酰亚胺-PEG20K-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:185,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白

<400> 59

Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala

20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 60
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-60
<220>
<221> MOD_RES
<222> (116)..(116)
<223> S-马来酰亚胺-PEG20K-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:185,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白
<400> 60
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60

Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 61
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-61
<220>
<221> MOD_RES
<222> (84)..(84)
<223> S-马来酰亚胺-PEG20K-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是:SEQ ID NO:189,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白
<400> 61
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu

100 105 110
Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 62
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-62
<220>
<221> MOD_RES
<222> (116)..(116)
<223> S-马来酰亚胺-PEG20K-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:186,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白
<400> 62
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140

Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 63
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-63
<220>
<221> MOD_RES
<222> (84)..(84)
<223> S-马来酰亚胺-PEG20K-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:187,通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白
<400> 63

Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 64
<211> 152
<212> PRT

<213> 人工序列
<220>
<223> 融合蛋白 G-64
<220>
<221> MOD_RES
<222> (116)..(116)
<223> S-马来酰亚胺-PEG20K-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是:SEQ ID NO:190,通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白
<400> 64

```
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1               5                  10                  15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
            20                  25                  30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
        35                  40                  45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
    50                  55                  60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65                  70                  75                  80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
                85                  90                  95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
            100                 105                 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
        115                 120                 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
    130                 135                 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145                 150
```

<210> 65
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-65
<220>
<221> MOD_RES

<222> (84)..(84)
<223> S-马来酰亚胺-PEG20K-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:188,通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白
<400> 65

Arg	Pro	Ser	Gly	Arg	Lys	Ser	Ser	Lys	Met	Gln	Ala	Phe	Arg	Ile	Trp
1				5				10					15		
Asp	Val	Asn	Gln	Lys	Thr	Phe	Tyr	Leu	Arg	Asn	Asn	Gln	Leu	Val	Ala
			20					25				30			
Gly	Tyr	Leu	Gln	Gly	Pro	Asn	Val	Asn	Leu	Glu	Glu	Lys	Ile	Asp	Val
		35					40					45			
Val	Pro	Ile	Glu	Pro	His	Ala	Leu	Phe	Leu	Gly	Ile	His	Gly	Gly	Lys
	50					55					60				
Met	Cys	Leu	Ser	Cys	Val	Lys	Ser	Gly	Asp	Glu	Thr	Arg	Leu	Gln	Leu
65					70					75					80
Glu	Ala	Val	Cys	Ile	Thr	Asp	Leu	Ser	Glu	Asn	Arg	Lys	Gln	Asp	Lys
				85					90					95	
Arg	Phe	Ala	Phe	Ile	Arg	Ser	Asp	Ser	Gly	Pro	Thr	Thr	Ser	Phe	Glu
			100					105					110		
Ser	Ala	Ala	Ser	Pro	Gly	Trp	Phe	Leu	Cys	Thr	Ala	Met	Glu	Ala	Asp
		115					120					125			
Gln	Pro	Val	Ser	Leu	Thr	Asn	Met	Pro	Asp	Glu	Gly	Val	Met	Val	Thr
	130					135					140				
Lys	Phe	Tyr	Phe	Gln	Glu	Asp	Glu								
145					150										

<210> 66
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-66
<220>
<221> MOD_RES
<222> (116)..(116)
<223> S-马来酰亚胺-PEG20K-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:188,通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白

<400> 66

Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 67

<211> 153

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 G-67

<220>

<221> MOD_RES

<222> (1)..(1)

<223> GLP-1受体结合多肽-S-马来酰亚胺-PEG20K-马来酰亚胺-S,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:185,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白

<400> 67

Cys Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
1 5 10 15
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
20 25 30

Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
35 40 45
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
50 55 60
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
65 70 75 80
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
85 90 95
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
100 105 110
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
115 120 125
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
130 135 140
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 68
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-68
<220>
<221> MOD_RES
<222> (1)..(1)
<223> PEG20K
<220>
<221> MOD_RES
<222> (116)..(116)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:185,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白;
<400> 68
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val

35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 69
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-69
<220>
<221> MOD_RES
<222> (1)..(1)
<223> PEG20K
<220>
<221> MOD_RES
<222> (84)..(84)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:186,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白
<400> 69
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45

Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 70
<211> 153
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-70
<220>
<221> MOD_RES
<222> (1)..(1)
<223> GLP-1受体结合多肽-S-马来酰亚胺-PEG20K-马来酰亚胺-S,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:189,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白

<400> 70
Cys Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
1 5 10 15
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
20 25 30
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
35 40 45
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
50 55 60
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
65 70 75 80
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp

85 90 95
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
100 105 110
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
115 120 125
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
130 135 140
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 71
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-71
<220>
<221> MOD_RES
<222> (84)..(84)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是:SEQ ID NO:191,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白
<400> 71
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125

Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 72
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-72
<220>
<221> MOD_RES
<222> (116)..(116)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:191,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白
<400> 72
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 73

<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-73
<220>
<221> MOD_RES
<222> (84)..(84)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:189,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白
<400> 73

Arg	Pro	Ser	Gly	Arg	Lys	Ser	Ser	Lys	Met	Gln	Ala	Phe	Arg	Ile	Trp
1				5				10					15		
Asp	Val	Asn	Gln	Lys	Thr	Phe	Tyr	Leu	Arg	Asn	Asn	Gln	Leu	Val	Ala
			20					25				30			
Gly	Tyr	Leu	Gln	Gly	Pro	Asn	Val	Asn	Leu	Glu	Glu	Lys	Ile	Asp	Val
		35					40					45			
Val	Pro	Ile	Glu	Pro	His	Ala	Leu	Phe	Leu	Gly	Ile	His	Gly	Gly	Lys
	50					55					60				
Met	Cys	Leu	Ser	Cys	Val	Lys	Ser	Gly	Asp	Glu	Thr	Arg	Leu	Gln	Leu
65					70					75					80
Glu	Ala	Val	Cys	Ile	Thr	Asp	Leu	Ser	Glu	Asn	Arg	Lys	Gln	Asp	Lys
				85					90					95	
Arg	Phe	Ala	Phe	Ile	Arg	Ser	Asp	Ser	Gly	Pro	Thr	Thr	Ser	Phe	Glu
			100					105					110		
Ser	Ala	Ala	Ser	Pro	Gly	Trp	Phe	Leu	Cys	Thr	Ala	Met	Glu	Ala	Asp
		115					120					125			
Gln	Pro	Val	Ser	Leu	Thr	Asn	Met	Pro	Asp	Glu	Gly	Val	Met	Val	Thr
	130					135					140				
Lys	Phe	Tyr	Phe	Gln	Glu	Asp	Glu								
145					150										

<210> 74
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-74

<220>
<221> MOD_RES
<222> (116)..(116)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:189,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白
<400> 74

Arg	Pro	Ser	Gly	Arg	Lys	Ser	Ser	Lys	Met	Gln	Ala	Phe	Arg	Ile	Trp
1				5				10					15		
Asp	Val	Asn	Gln	Lys	Thr	Phe	Tyr	Leu	Arg	Asn	Asn	Gln	Leu	Val	Ala
			20					25					30		
Gly	Tyr	Leu	Gln	Gly	Pro	Asn	Val	Asn	Leu	Glu	Glu	Lys	Ile	Asp	Val
		35					40					45			
Val	Pro	Ile	Glu	Pro	His	Ala	Leu	Phe	Leu	Gly	Ile	His	Gly	Gly	Lys
	50					55					60				
Met	Cys	Leu	Ser	Cys	Val	Lys	Ser	Gly	Asp	Glu	Thr	Arg	Leu	Gln	Leu
65					70					75					80
Glu	Ala	Val	Asn	Ile	Thr	Asp	Leu	Ser	Glu	Asn	Arg	Lys	Gln	Asp	Lys
				85					90					95	
Arg	Phe	Ala	Phe	Ile	Arg	Ser	Asp	Ser	Gly	Pro	Thr	Thr	Ser	Phe	Glu
			100					105					110		
Ser	Ala	Ala	Cys	Pro	Gly	Trp	Phe	Leu	Cys	Thr	Ala	Met	Glu	Ala	Asp
		115					120					125			
Gln	Pro	Val	Ser	Leu	Thr	Asn	Met	Pro	Asp	Glu	Gly	Val	Met	Val	Thr
	130					135					140				
Lys	Phe	Tyr	Phe	Gln	Glu	Asp	Glu								
145					150										

<210> 75
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-75
<220>
<221> MOD_RES
<222> (84)..(84)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID

NO:190,通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白

<400> 75

Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 76

<211> 152

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 G-76

<220>

<221> MOD_RES

<222> (116)..(116)

<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:190,通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白

<400> 76

Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15

Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 77
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-77
<220>
<221> MOD_RES
<222> (84)..(84)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是:SEQ ID NO:192,通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白
<400> 77
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys

50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 78
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-78
<220>
<221> MOD_RES
<222> (116)..(116)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:192,通过半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白
<400> 78
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95

Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 79
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-79
<220>
<221> MOD_RES
<222> (84)..(84)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是:SEQ ID NO:193,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白

<400> 79
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr

130 135 140

Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 80
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-80
<220>
<221> MOD_RES
<222> (116)..(116)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GLP-1受体结合多肽,S是半胱氨酸侧链的硫原子,其中GLP-1受体结合多肽的序列是SEQ ID NO:193,通过末端半胱氨酸侧链巯基与马来酰亚胺反应,连接白介素-1受体拮抗蛋白
<400> 80

Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 81
<211> 796

<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-81
<400> 81

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        35                  40                  45
Ser Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly
    50                  55                  60
Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu
65                  70                  75                  80
Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr
                85                  90                  95
Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp
            100                 105                 110
Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr
        115                 120                 125
Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu
    130                 135                 140
Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn
145                 150                 155                 160
Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe
                165                 170                 175
His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala
            180                 185                 190
Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys
        195                 200                 205
Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala
    210                 215                 220
Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala
225                 230                 235                 240
Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly
                245                 250                 255
Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe
            260                 265                 270
```

Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr
275 280 285
Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp
290 295 300
Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile
305 310 315 320
Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser
325 330 335
His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro
340 345 350
Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr
355 360 365
Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala
370 375 380
Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys
385 390 395 400
Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His
405 410 415
Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu
420 425 430
Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
435 440 445
Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
450 455 460
Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
465 470 475 480
Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
485 490 495
Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
500 505 510
His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
515 520 525
Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
530 535 540
Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
545 550 555 560
Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
565 570 575
Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln

580 585 590
Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
595 600 605
Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
610 615 620
Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Gly Gly Gly Ser Gly
625 630 635 640
Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala
645 650 655
Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn
660 665 670
Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu
675 680 685
Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile
690 695 700
His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr
705 710 715 720
Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg
725 730 735
Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr
740 745 750
Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala
755 760 765
Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly
770 775 780
Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
785 790 795

<210> 82
<211> 796
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-82
<400> 82
His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly

35 40 45

Ser Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly

50 55 60

Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu

65 70 75 80

Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr

85 90 95

Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp

100 105 110

Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr

115 120 125

Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu

130 135 140

Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn

145 150 155 160

Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe

165 170 175

His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala

180 185 190

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys

195 200 205

Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala

210 215 220

Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala

225 230 235 240

Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly

245 250 255

Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe

260 265 270

Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr

275 280 285

Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp

290 295 300

Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile

305 310 315 320

Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser

325 330 335

His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro

340 345 350

Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr
355 360 365
Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala
370 375 380
Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys
385 390 395 400
Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His
405 410 415
Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu
420 425 430
Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
435 440 445
Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
450 455 460
Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
465 470 475 480
Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
485 490 495
Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
500 505 510
His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
515 520 525
Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
530 535 540
Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
545 550 555 560
Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
565 570 575
Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
580 585 590
Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
595 600 605
Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
610 615 620
Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Gly Gly Gly Ser Gly
625 630 635 640
Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala
645 650 655
Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn

660 665 670
Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu
675 680 685
Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile
690 695 700
His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr
705 710 715 720
Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg
725 730 735
Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr
740 745 750
Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala
755 760 765
Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly
770 775 780
Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
785 790 795

<210> 83
<211> 796
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-83
<400> 83
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
50 55 60
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
85 90 95
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
100 105 110
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln

115 120 125

Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp

130 135 140

Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe

145 150 155 160

Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala

165 170 175

Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val

180 185 190

Thr Lys Phe Tyr Phe Gln Glu Asp Glu Gly Gly Gly Gly Ser Gly Gly

195 200 205

Gly Gly Ser Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp

210 215 220

Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln

225 230 235 240

Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu

245 250 255

Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn

260 265 270

Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val

275 280 285

Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys

290 295 300

Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn

305 310 315 320

Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr

325 330 335

Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu

340 345 350

Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe

355 360 365

Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp

370 375 380

Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly

385 390 395 400

Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys

405 410 415

Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln

420 425 430

Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp
435 440 445
Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys
450 455 460
Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp
465 470 475 480
Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu
485 490 495
Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp
500 505 510
Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys
515 520 525
Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu
530 535 540
Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu
545 550 555 560
Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp
565 570 575
Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val
580 585 590
Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln
595 600 605
Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys
610 615 620
Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn
625 630 635 640
Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg
645 650 655
Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys
660 665 670
Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys
675 680 685
Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val
690 695 700
Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe
705 710 715 720
His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys
725 730 735
Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys

740 745 750
Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys
755 760 765
Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys
770 775 780
Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
785 790 795

<210> 84
<211> 796
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 G-84
<400> 84

His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
50 55 60
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
85 90 95
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
100 105 110
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
115 120 125
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
130 135 140
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
145 150 155 160
Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
165 170 175
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
180 185 190
Thr Lys Phe Tyr Phe Gln Glu Asp Glu Gly Gly Gly Gly Ser Gly Gly

195 200 205

Gly Gly Ser Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp

210 215 220

Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln

225 230 235 240

Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu

245 250 255

Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn

260 265 270

Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val

275 280 285

Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys

290 295 300

Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn

305 310 315 320

Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr

325 330 335

Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu

340 345 350

Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe

355 360 365

Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp

370 375 380

Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly

385 390 395 400

Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys

405 410 415

Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln

420 425 430

Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp

435 440 445

Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys

450 455 460

Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp

465 470 475 480

Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu

485 490 495

Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp

500 505 510

Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys
515 520 525
Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu
530 535 540
Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu
545 550 555 560
Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp
565 570 575
Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val
580 585 590
Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln
595 600 605
Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys
610 615 620
Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn
625 630 635 640
Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg
645 650 655
Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys
660 665 670
Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys
675 680 685
Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val
690 695 700
Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe
705 710 715 720
His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys
725 730 735
Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys
740 745 750
Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys
755 760 765
Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys
770 775 780
Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
785 790 795

<210> 85
<211> 215
<212> PRT

<213> 人工序列
<220>
<223> 融合蛋白 IN-1
<400> 85

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Ser
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Arg
50 55 60
Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp
65 70 75 80
Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly
85 90 95
Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val
100 105 110
Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met
115 120 125
Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu
130 135 140
Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg
145 150 155 160
Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser
165 170 175
Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln
180 185 190
Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys
195 200 205
Phe Tyr Phe Gln Glu Asp Glu
210 215

<210> 86
<211> 215
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-2
<400> 86

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Ser
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Arg
50 55 60
Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp
65 70 75 80
Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly
85 90 95
Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val
100 105 110
Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met
115 120 125
Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu
130 135 140
Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg
145 150 155 160
Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser
165 170 175
Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln
180 185 190
Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys
195 200 205
Phe Tyr Phe Gln Glu Asp Glu
210 215

<210> 87
<211> 215
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-3
<400> 87

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Ser
20 25 30

Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Arg
50 55 60
Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp
65 70 75 80
Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly
85 90 95
Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val
100 105 110
Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met
115 120 125
Ser Leu Ser Ser Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu
130 135 140
Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg
145 150 155 160
Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser
165 170 175
Ala Ala Ser Pro Gly Trp Phe Leu Ser Thr Ala Met Glu Ala Asp Gln
180 185 190
Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys
195 200 205
Phe Tyr Phe Gln Glu Asp Glu
210 215

<210> 88
<211> 220
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-4
<400> 88

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Ser
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly
50 55 60

Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala
65 70 75 80
Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn
85 90 95
Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu
100 105 110
Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile
115 120 125
His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr
130 135 140
Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg
145 150 155 160
Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr
165 170 175
Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala
180 185 190
Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly
195 200 205
Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
210 215 220

<210> 89
<211> 220
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-5
<400> 89

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Ser
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly
50 55 60
Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala
65 70 75 80
Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn
85 90 95

Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu
100 105 110
Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile
115 120 125
His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr
130 135 140
Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg
145 150 155 160
Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr
165 170 175
Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala
180 185 190
Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly
195 200 205
Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
210 215 220

<210> 90
<211> 220
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-6
<400> 90

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Ser
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly
50 55 60
Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala
65 70 75 80
Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn
85 90 95
Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu
100 105 110
Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile
115 120 125

His Gly Gly Lys Met Ser Leu Ser Ser Val Lys Ser Gly Asp Glu Thr
130 135 140
Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg
145 150 155 160
Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr
165 170 175
Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Ser Thr Ala
180 185 190
Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly
195 200 205
Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
210 215 220

<210> 91
<211> 225
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-7
<400> 91

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Ser
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly
50 55 60
Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser
65 70 75 80
Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe
85 90 95
Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn
100 105 110
Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala
115 120 125
Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys
130 135 140
Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp
145 150 155 160

Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser
165 170 175
Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp
180 185 190
Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn
195 200 205
Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp
210 215 220
Glu
225

<210> 92
<211> 225
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-8
<400> 92

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Ser
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly
50 55 60
Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser
65 70 75 80
Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe
85 90 95
Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn
100 105 110
Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala
115 120 125
Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys
130 135 140
Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp
145 150 155 160
Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser
165 170 175

Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly Trp
180 185 190
Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn
195 200 205
Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp
210 215 220
Glu
225

<210> 93
<211> 225
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-9
<400> 93
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Ser
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly
50 55 60
Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser
65 70 75 80
Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe
85 90 95
Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn
100 105 110
Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala
115 120 125
Leu Phe Leu Gly Ile His Gly Gly Lys Met Ser Leu Ser Ser Val Lys
130 135 140
Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp
145 150 155 160
Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser
165 170 175
Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly Trp
180 185 190

Phe Leu Ser Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn
195 200 205
Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp
210 215 220
Glu
225

<210> 94
<211> 230
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-10
<400> 94

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Ser
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly
50 55 60
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro
65 70 75 80
Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val
85 90 95
Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr
100 105 110
Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro
115 120 125
Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys
130 135 140
Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala
145 150 155 160
Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe
165 170 175
Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala
180 185 190
Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro
195 200 205

Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe
210 215 220
Tyr Phe Gln Glu Asp Glu
225 230
<210> 95
<211> 230
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-11
<400> 95
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Ser
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly
50 55 60
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro
65 70 75 80
Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val
85 90 95
Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr
100 105 110
Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro
115 120 125
Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys
130 135 140
Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala
145 150 155 160
Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe
165 170 175
Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala
180 185 190
Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro
195 200 205
Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe
210 215 220

Tyr Phe Gln Glu Asp Glu
225 230

<210> 96
<211> 230
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-12
<400> 96

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Ser
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly
50 55 60
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro
65 70 75 80
Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val
85 90 95
Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr
100 105 110
Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro
115 120 125
Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Ser
130 135 140
Leu Ser Ser Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala
145 150 155 160
Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe
165 170 175
Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala
180 185 190
Ala Ser Pro Gly Trp Phe Leu Ser Thr Ala Met Glu Ala Asp Gln Pro
195 200 205
Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe
210 215 220
Tyr Phe Gln Glu Asp Glu
225 230

<210> 97
<211> 210
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-13
<400> 97

```
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1               5                  10                  15
Leu Val Cys Gly Glu Arg Gly Phe Phe Gly Ser Gly Ser Ser Ser Ala
            20                  25                  30
Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
        35                  40                  45
Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Arg Pro Ser Gly Arg Lys
    50                  55                  60
Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr
65                  70                  75                  80
Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro
                85                  90                  95
Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His
            100                 105                 110
Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val
        115                 120                 125
Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr
    130                 135                 140
Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg
145                 150                 155                 160
Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly
                165                 170                 175
Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr
            180                 185                 190
Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu
        195                 200                 205
Asp Glu
    210
```

<210> 98
<211> 210
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白 IN-14
<400> 98

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Gly Ser Gly Ser Ser Ser Ala
20 25 30
Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45
Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Arg Pro Ser Gly Arg Lys
50 55 60
Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr
65 70 75 80
Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro
85 90 95
Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His
100 105 110
Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val
115 120 125
Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr
130 135 140
Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg
145 150 155 160
Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly
165 170 175
Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr
180 185 190
Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu
195 200 205
Asp Glu
210

<210> 99
<211> 210
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-15
<400> 99

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr

1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Gly Ser Gly Ser Ser Ser Ala
20 25 30
Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45
Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Arg Pro Ser Gly Arg Lys
50 55 60
Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr
65 70 75 80
Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro
85 90 95
Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His
100 105 110
Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Ser Leu Ser Ser Val
115 120 125
Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr
130 135 140
Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg
145 150 155 160
Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly
165 170 175
Trp Phe Leu Ser Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr
180 185 190
Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu
195 200 205
Asp Glu
210

<210> 100
<211> 215
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-16
<400> 100
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Gly Ser Gly Ser Ser Ser Ala
20 25 30
Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys

35 40 45

Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly Gly Gly Gly Ser Arg
50 55 60

Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp
65 70 75 80

Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly
85 90 95

Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val
100 105 110

Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met
115 120 125

Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu
130 135 140

Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg
145 150 155 160

Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser
165 170 175

Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln
180 185 190

Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys
195 200 205

Phe Tyr Phe Gln Glu Asp Glu
210 215

<210> 101
<211> 215
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-17
<400> 101

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Gly Ser Gly Ser Ser Ser Ala
20 25 30

Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45

Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly Gly Gly Gly Ser Arg
50 55 60

Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp

65 70 75 80
Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly
85 90 95
Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val
100 105 110
Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met
115 120 125
Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu
130 135 140
Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg
145 150 155 160
Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser
165 170 175
Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln
180 185 190
Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys
195 200 205
Phe Tyr Phe Gln Glu Asp Glu
210 215

<210> 102
<211> 215
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-18
<400> 102

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Gly Ser Gly Ser Ser Ser Ala
20 25 30
Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45
Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly Gly Gly Gly Ser Arg
50 55 60
Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp
65 70 75 80
Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly
85 90 95
Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val

100 105 110
Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met
115 120 125
Ser Leu Ser Ser Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu
130 135 140
Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg
145 150 155 160
Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser
165 170 175
Ala Ala Ser Pro Gly Trp Phe Leu Ser Thr Ala Met Glu Ala Asp Gln
180 185 190
Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys
195 200 205
Phe Tyr Phe Gln Glu Asp Glu
210 215

<210> 103
<211> 220
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-19
<400> 103
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Gly Ser Gly Ser Ser Ser Ala
20 25 30
Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45
Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly Gly Gly Gly Ser Gly
50 55 60
Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala
65 70 75 80
Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn
85 90 95
Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu
100 105 110
Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile
115 120 125
His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr

130 135 140
Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg
145 150 155 160
Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr
165 170 175
Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala
180 185 190
Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly
195 200 205
Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
210 215 220

<210> 104
<211> 220
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-20
<400> 104
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Gly Ser Gly Ser Ser Ser Ala
20 25 30
Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45
Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly Gly Gly Gly Ser Gly
50 55 60
Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala
65 70 75 80
Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn
85 90 95
Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu
100 105 110
Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile
115 120 125
His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr
130 135 140
Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg
145 150 155 160
Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr

165 170 175
Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala
180 185 190
Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly
195 200 205
Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
210 215 220

<210> 105
<211> 220
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-21
<400> 105

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Gly Ser Gly Ser Ser Ser Ala
20 25 30
Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45
Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly Gly Gly Gly Ser Gly
50 55 60
Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala
65 70 75 80
Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn
85 90 95
Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu
100 105 110
Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile
115 120 125
His Gly Gly Lys Met Ser Leu Ser Ser Val Lys Ser Gly Asp Glu Thr
130 135 140
Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg
145 150 155 160
Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr
165 170 175
Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Ser Thr Ala
180 185 190
Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly

195 200 205

Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
210 215 220

<210> 106
<211> 225
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-22
<400> 106

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Gly Ser Gly Ser Ser Ser Ala
20 25 30
Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45
Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly Gly Gly Gly Ser Gly
50 55 60
Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser
65 70 75 80
Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe
85 90 95
Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn
100 105 110
Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala
115 120 125
Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys
130 135 140
Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp
145 150 155 160
Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser
165 170 175
Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp
180 185 190
Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn
195 200 205
Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp
210 215 220
Glu

225

<210> 107

<211> 225

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 IN-23

<400> 107

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Gly Ser Gly Ser Ser Ser Ala
20 25 30
Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45
Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly Gly Gly Gly Ser Gly
50 55 60
Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser
65 70 75 80
Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe
85 90 95
Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn
100 105 110
Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala
115 120 125
Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys
130 135 140
Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp
145 150 155 160
Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser
165 170 175
Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly Trp
180 185 190
Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn
195 200 205
Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp
210 215 220
Glu
225

<210> 108

<211> 225
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-24
<400> 108

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Gly Ser Gly Ser Ser Ser Ala
20 25 30
Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45
Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly Gly Gly Gly Ser Gly
50 55 60
Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser
65 70 75 80
Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe
85 90 95
Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn
100 105 110
Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala
115 120 125
Leu Phe Leu Gly Ile His Gly Gly Lys Met Ser Leu Ser Ser Val Lys
130 135 140
Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp
145 150 155 160
Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser
165 170 175
Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly Trp
180 185 190
Phe Leu Ser Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn
195 200 205
Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp
210 215 220
Glu
225

<210> 109
<211> 225
<212> PRT

<213> 人工序列
<220>
<223> 融合蛋白 IN-25
<220>
<221> MOD_RES
<222> (189)..(189)
<223> S-马来酰亚胺-(CH2)4-NH-(Nα-(HOOC(CH2)14CO)-γ-Glu),S是半胱氨酸侧链的硫原子
<400> 109

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Ser
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly
50 55 60
Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser
65 70 75 80
Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe
85 90 95
Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn
100 105 110
Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala
115 120 125
Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys
130 135 140
Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp
145 150 155 160
Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser
165 170 175
Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp
180 185 190
Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn
195 200 205
Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp
210 215 220
Glu
225

<210> 110
<211> 225
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-26
<220>
<221> MOD_RES
<222> (157)..(157)
<223> S-CH2-CONH-(CH2CH2O)2-(CH2)2-NH-(Nα-(HOOC(CH2)14CO)-γ-Glu),S是半胱氨酸侧链的硫原子
<400> 110

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Ser
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly
50 55 60
Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser
65 70 75 80
Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe
85 90 95
Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn
100 105 110
Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala
115 120 125
Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys
130 135 140
Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Cys Ile Thr Asp
145 150 155 160
Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser
165 170 175
Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly Trp
180 185 190
Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn
195 200 205
Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp

210 215 220

Glu

225

<210> 111

<211> 220

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 IN-27

<220>

<221> MOD_RES

<222> (184)..(184)

<223> S-CH2-CONH-PEG20K,S是半胱氨酸侧链的硫原子

<400> 111

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Gly Ser Gly Ser Ser Ser Ala
20 25 30
Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45
Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly Gly Gly Gly Ser Gly
50 55 60
Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala
65 70 75 80
Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn
85 90 95
Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu
100 105 110
Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile
115 120 125
His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr
130 135 140
Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg
145 150 155 160
Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr
165 170 175
Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala
180 185 190
Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly

195 200 205

Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
210 215 220

<210> 112
<211> 220
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-28
<220>
<221> MOD_RES
<222> (152)..(152)
<223> S-马来酰亚胺-(CH2)15- COOH,S是半胱氨酸侧链的硫原子
<400> 112

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Gly Ser Gly Ser Ser Ser Ala
20 25 30
Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45
Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly Gly Gly Gly Ser Gly
50 55 60
Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala
65 70 75 80
Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn
85 90 95
Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu
100 105 110
Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile
115 120 125
His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr
130 135 140
Arg Leu Gln Leu Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg
145 150 155 160
Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr
165 170 175
Thr Ser Phe Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala
180 185 190
Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly

195 200 205

Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
210 215 220

<210> 113

<211> 63

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 IN-29

<220>

<221> MOD_RES

<222> (32)..(32)

<223> Nε-PEG12-马来酰亚胺-IL-1ra,其中IL-1ra的序列为SEQ ID NO:194,连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与胰岛素受体结合多肽赖氨酸侧链的氨基反应,马来酰亚胺与SEQ ID NO:194的116位的半胱氨酸侧链巯基反应。

<400> 113

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Arg Thr Gly Lys
20 25 30

Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 114

<211> 63

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 IN-30

<220>

<221> MOD_RES

<222> (32)..(32)

<223> Nε-PEG12-马来酰亚胺-白介素-1受体拮抗蛋白,其中白介素-1受体拮抗蛋白的序列为SEQ ID NO:195,连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与胰岛素受体结合多肽赖氨酸侧链的氨基反应,马来酰亚胺与SEQ ID

<400> 114

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Arg Thr Gly Lys
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 115
<211> 63
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-31
<220>
<221> MOD_RES
<222> (32)..(32)
<223> Nε-PEG20K-马来酰亚胺-IL-1ra,其中IL-1ra的序列为SEQ ID NO:194,连接基马来酰亚胺-PEG20K-NHS的N-羟基琥珀酰亚胺与胰岛素受体结合多肽赖氨酸侧链的氨基反应,马来酰亚胺与SEQ ID NO:194的116位的半胱氨酸侧链巯基反应
<400> 115

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Arg Thr Gly Lys
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 116
<211> 63
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-32
<220>
<221> MOD_RES
<222> (32)..(32)

<223> Nε-PEG20K-马来酰亚胺-白介素-1受体拮抗蛋白,其中白介素-1受体拮抗蛋白的序列为SEQ ID NO:195,连接基马来酰亚胺-PEG20K-NHS的N-羟基琥珀酰亚胺与胰岛素受体结合多肽赖氨酸侧链的氨基反应,马来酰亚胺与SEQ ID NO:194的116位的半胱氨酸侧链巯基反应

<400> 116

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Arg Thr Gly Lys
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 117

<211> 63

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 IN-33

<220>

<221> MOD_RES

<222> (1)..(1)

<223> Nα-(Nα-(HOOC(CH2)14CO)-γ-L-Glu)

<220>

<221> MOD_RES

<222> (32)..(32)

<223> Nε-PEG12-马来酰亚胺-IL-1ra,其中IL-1ra的序列为SEQ ID NO:194,连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与胰岛素受体结合多肽赖氨酸侧链的氨基反应,马来酰亚胺与SE ID NO:194的116位的半胱氨酸侧链巯基反应

<400> 117

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Arg Thr Gly Lys
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 118
<211> 63
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-34
<220>
<221> MOD_RES
<222> (1)..(1)
<223> Nα-(Nα-(HOOC(CH2)16CO)-γ-L-Glu)
<220>
<221> MOD_RES
<222> (32)..(32)
<223> Nε-PEG12-马来酰亚胺-白介素-1受体拮抗蛋白,其中白介素-1受体拮抗蛋白的序列为SEQ ID NO:195,连接基马来酰亚胺-PEG12-NHS的N-羟基琥珀酰亚胺与胰岛素受体结合多肽赖氨酸侧链的氨基反应,马来酰亚胺与SEQ ID
<400> 118

Phe	Val	Asn	Gln	His	Leu	Cys	Gly	Ser	His	Leu	Val	Glu	Ala	Leu	Tyr
1				5				10						15	
Leu	Val	Cys	Gly	Glu	Arg	Gly	Phe	Phe	Tyr	Thr	Pro	Arg	Thr	Gly	Lys
			20					25					30		
Gly	Ser	Ser	Ser	Ala	Ala	Ala	Pro	Gln	Thr	Gly	Ile	Val	Glu	Gln	Cys
		35					40					45			
Cys	Thr	Ser	Ile	Cys	Ser	Leu	Tyr	Gln	Leu	Glu	Asn	Tyr	Cys	Asn	
	50					55					60				

<210> 119
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-35
<220>
<221> MOD_RES
<222> (116)..(116)
<223> S-马来酰亚胺-PEG12-人胰岛素,S是半胱氨酸侧链的硫原子
<400> 119

Arg	Pro	Ser	Gly	Arg	Lys	Ser	Ser	Lys	Met	Gln	Ala	Phe	Arg	Ile	Trp
1				5				10						15	

Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 120
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-36
<220>
<221> MOD_RES
<222> (116)..(116)
<223> S-马来酰亚胺-PEG12-胰岛素受体结合多肽,S是半胱氨酸侧链的硫原子
<400> 120
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80

Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 121
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-37
<220>
<221> MOD_RES
<222> (116)..(116)
<223> S-马来酰亚胺-PEG20K-人胰岛素,S是半胱氨酸侧链的硫原子
<400> 121
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140

Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 122
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-38
<220>
<221> MOD_RES
<222> (84)..(84)
<223> S-马来酰亚胺-PEG 12 -人胰岛素,S是半胱氨酸侧链的硫原子
<400> 122
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 123
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-39

<220>
<221> MOD_RES
<222> (84)..(84)
<223> S-马来酰亚胺-PEG 20K-人胰岛素,S是半胱氨酸侧链的硫原子
<400> 123
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150
<210> 124
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-40
<220>
<221> MOD_RES
<222> (84)..(84)
<223> S-马来酰亚胺-PEG12 -胰岛素受体结合多肽,S是半胱氨酸侧链的硫原子
<400> 124
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala

20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 125
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-41
<220>
<221> MOD_RES
<222> (116)..(116)
<223> S-马来酰亚胺-PEG12-人胰岛素desB30T,S是半胱氨酸侧链的硫原子
<400> 125
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys

85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 126
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-42
<220>
<221> MOD_RES
<222> (116)..(116)
<223> S-马来酰亚胺-PEG2OK-人胰岛素desB30T,S是半胱氨酸侧链的硫原子
<400> 126
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu

145 150

<210> 127

<211> 152

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 IN-43

<220>

<221> MOD_RES

<222> (84)..(84)

<223> S-马来酰亚胺-PEG 12-人胰岛素desB30T,S是半胱氨酸侧链的硫原子

<400> 127

Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15

Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30

Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45

Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60

Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80

Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95

Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110

Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125

Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140

Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 128

<211> 152

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 IN-44

<220>

<221> MOD_RES
<222> (84)..(84)
<223> S-马来酰亚胺-PEG 20K-人胰岛素desB30T,S是半胱氨酸侧链的硫原子
<400> 128

Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 129
<211> 64
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-45
<220>
<221> MOD_RES
<222> (64)..(64)
<223> Nε-PEG12-马来酰亚胺-IL-1ra,IL-1ra的序列是SEQ ID NO:194
<400> 129

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Arg Thr Gly Ser
20 25 30

Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Lys
50 55 60

<210> 130
<211> 64
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-46
<220>
<221> MOD_RES
<222> (64)..(64)
<223> Nε-PEG20K-马来酰亚胺-IL-1ra,其中IL-1ra的序列是:SEQ ID NO:194
<400> 130
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Arg Thr Gly Ser
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Lys
50 55 60

<210> 131
<211> 64
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-47
<220>
<221> MOD_RES
<222> (64)..(64)
<223> Nε-PEG12-马来酰亚胺-白介素-1受体拮抗蛋白,白介素-1受体拮抗蛋白的序列是:SEQ ID NO:195
<400> 131
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Arg Thr Gly Ser
20 25 30

Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Lys
50 55 60

<210> 132
<211> 64
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-48
<220>
<221> MOD_RES
<222> (64)..(64)
<223> Nε-PEG20K-马来酰亚胺-白介素-1受体拮抗蛋白,白介素-1受体拮抗蛋白的序列是:SEQ ID NO:195
<400> 132

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Arg Thr Gly Ser
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Lys
50 55 60

<210> 133
<211> 63
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-49
<220>
<221> MOD_RES
<222> (1)..(1)
<223> Nα-PEG12-马来酰亚胺-IL-1ra,其中IL-1ra的序列是SEQ ID NO:196
<400> 133

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Arg Thr Gly Ser
20 25 30

Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 134
<211> 63
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-50
<220>
<221> MOD_RES
<222> (1)..(1)
<223> Nα-PEG20K-马来酰亚胺- IL-1ra,IL-1ra的序列是:SEQ ID NO:196
<400> 134
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Arg Thr Gly Ser
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 135
<211> 63
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-51
<220>
<221> MOD_RES
<222> (32)..(32)
<223> Nε-PEG12-马来酰亚胺-白介素-1受体拮抗蛋白,白介素-1受体拮抗蛋白的序列是:SEQ ID NO:196
<400> 135
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Arg Thr Gly Lys
20 25 30

Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 136
<211> 63
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-52
<220>
<221> MOD_RES
<222> (32)..(32)
<223> Nε-PEG20K-马来酰亚胺-白介素-1受体拮抗蛋白,白介素-1受体拮抗蛋白的序列是:SEQ ID NO:196
<400> 136
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Arg Thr Gly Lys
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 137
<211> 63
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-53
<220>
<221> MOD_RES
<222> (38)..(38)
<223> Nε-PEG12-马来酰亚胺-白介素-1受体拮抗蛋白,白介素-1受体拮抗蛋白的序列是:SEQ ID NO:196
<400> 137
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Arg Thr Gly Ser

20 25 30
Gly Ser Ser Ser Ala Lys Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60
<210> 138
<211> 63
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-54
<220>
<221> MOD_RES
<222> (38)..(38)
<223> Nε-PEG20K-马来酰亚胺-白介素-1受体拮抗蛋白,白介素-1受体拮抗蛋白的序列是:SEQ ID NO:196
<400> 138
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Arg Thr Gly Ser
20 25 30
Gly Ser Ser Ser Ala Lys Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60
<210> 139
<211> 58
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-55
<220>
<221> MOD_RES
<222> (33)..(33)
<223> Nε-PEG12-马来酰亚胺-IL-1ra,IL-1ra的序列为SEQ ID NO:194
<400> 139
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Gly Ser Gly Ser Ser Ser Ala

20 25 30
Lys Ala Pro Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45
Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55
<210> 140
<211> 58
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-56
<220>
<221> MOD_RES
<222> (33)..(33)
<223> Nε-PEG12-马来酰亚胺-白介素-1受体拮抗蛋白;白介素-1受体拮抗蛋白的序列为:SEQ ID NO:195
<400> 140
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Gly Ser Gly Ser Ser Ser Ala
20 25 30
Lys Ala Pro Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45
Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55
<210> 141
<211> 153
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-57
<220>
<221> MOD_RES
<222> (1)..(1)
<223> S-马来酰亚胺-PEG12-人胰岛素,S是半胱氨酸侧链的硫原子
<400> 141
Cys Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
1 5 10 15
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val

20 25 30
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
35 40 45
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
50 55 60
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
65 70 75 80
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
85 90 95
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
100 105 110
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
115 120 125
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
130 135 140
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 142
<211> 153
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-58
<220>
<221> MOD_RES
<222> (1)..(1)
<223> S-马来酰亚胺-PEG12-胰岛素受体结合多肽,S是半胱氨酸侧链的硫原子
<400> 142
Cys Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
1 5 10 15
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
20 25 30
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
35 40 45
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
50 55 60
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
65 70 75 80
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp

85 90 95
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
100 105 110
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
115 120 125
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
130 135 140
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 143
<211> 153
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-59
<220>
<221> MOD_RES
<222> (1)..(1)
<223> S-马来酰亚胺-PEG12-人胰岛素desB30T,S是半胱氨酸侧链的硫原子
<400> 143
Cys Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
1 5 10 15
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
20 25 30
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
35 40 45
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
50 55 60
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
65 70 75 80
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
85 90 95
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
100 105 110
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
115 120 125
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
130 135 140
Thr Lys Phe Tyr Phe Gln Glu Asp Glu

145 150

<210> 144

<211> 154

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 IN-60

<220>

<221> MOD_RES

<222> (154)..(154)

<223> S-马来酰亚胺-PEG12-人胰岛素,S是半胱氨酸侧链的硫原子

<400> 144

Met Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
1 5 10 15

Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
20 25 30

Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
35 40 45

Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
50 55 60

Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
65 70 75 80

Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
85 90 95

Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
100 105 110

Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
115 120 125

Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
130 135 140

Thr Lys Phe Tyr Phe Gln Glu Asp Glu Cys
145 150

<210> 145

<211> 154

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 IN-61

<220>

<221> MOD_RES
<222> (154)..(154)
<223> S-马来酰亚胺-PEG12-人胰岛素desB30T,S是半胱氨酸侧链的硫原子
<400> 145

```
Met Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
1               5                  10                  15
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
            20                  25                  30
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
        35                  40                  45
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
    50                  55                  60
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
65                  70                  75                  80
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
                85                  90                  95
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
            100                 105                 110
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
        115                 120                 125
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
    130                 135                 140
Thr Lys Phe Tyr Phe Gln Glu Asp Glu Cys
145                 150
```

<210> 146
<211> 225
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-62
<400> 146

```
Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1               5                  10                  15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
            20                  25                  30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
        35                  40                  45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
    50                  55                  60
```

Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu Gly Gly Gly Gly Ser Gly Gly Gly
145 150 155 160
Gly Ser Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala
165 170 175
Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr
180 185 190
Gly Ser Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu
195 200 205
Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys
210 215 220
Asn
225

<210> 147
<211> 225
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-63
<400> 147

Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80

Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu Gly Gly Gly Gly Ser Gly Gly Gly
145 150 155 160
Gly Ser Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala
165 170 175
Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr
180 185 190
Gly Ser Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu
195 200 205
Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys
210 215 220
Asn
225

<210> 148
<211> 225
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-64
<400> 148

Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Ser Leu Ser Ser Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95

Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Ser Pro Gly Trp Phe Leu Ser Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu Gly Gly Gly Gly Ser Gly Gly Gly
145 150 155 160
Gly Ser Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala
165 170 175
Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr
180 185 190
Gly Ser Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu
195 200 205
Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys
210 215 220
Asn
225

<210> 149
<211> 225
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-65
<400> 149

Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110

Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu Gly Gly Gly Gly Ser Gly Gly Gly
145 150 155 160
Gly Ser Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala
165 170 175
Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr
180 185 190
Gly Ser Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu
195 200 205
Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys
210 215 220
Asn
225

<210> 150
<211> 232
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-66
<400> 150

Met Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
1 5 10 15
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
20 25 30
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
35 40 45
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
50 55 60
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
65 70 75 80
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
85 90 95
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
100 105 110
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
115 120 125

Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
130 135 140
Thr Lys Phe Tyr Phe Gln Glu Asp Glu Gly Gly Gly Gly Ser Cys Gly
145 150 155 160
Gly Gly Gly Ser Gly Gly Gly Gly Ser Phe Val Asn Gln His Leu Cys
165 170 175
Gly Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly
180 185 190
Phe Phe Tyr Thr Pro Lys Thr Gly Ser Gly Ser Ser Ser Ala Ala Ala
195 200 205
Pro Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu
210 215 220
Tyr Gln Leu Glu Asn Tyr Cys Asn
225 230

<210> 151
<211> 231
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-67
<400> 151

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Ser
20 25 30
Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45
Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Gly
50 55 60
Gly Gly Gly Ser Gly Gly Gly Gly Ser Cys Gly Gly Gly Gly Ser Arg
65 70 75 80
Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp
85 90 95
Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly
100 105 110
Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val
115 120 125
Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met
130 135 140

Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu
145 150 155 160
Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg
165 170 175
Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser
180 185 190
Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln
195 200 205
Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys
210 215 220
Phe Tyr Phe Gln Glu Asp Glu
225 230

<210> 152
<211> 820
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-68
<400> 152

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15
Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30
Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45
Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60
Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80
Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95
Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110
Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125
Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140
Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175
Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190
Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205
Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220
Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240
Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255
Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270
Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285
Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300
Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320
Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335
Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350
Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365
Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380
Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400
Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415
Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430
Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445
Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460
Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser

465 470 475 480
Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495
Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510
Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525
Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540
Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560
Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575
Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Gly Gly Gly Ser Gly Gly
580 585 590
Gly Gly Ser Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu
595 600 605
Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys
610 615 620
Thr Gly Ser Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly Ile Val
625 630 635 640
Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr
645 650 655
Cys Asn Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly
660 665 670
Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln
675 680 685
Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln
690 695 700
Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu
705 710 715 720
Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser
725 730 735
Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn
740 745 750
Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe
755 760 765
Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys
770 775 780

Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser
785 790 795 800
Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe
805 810 815
Gln Glu Asp Glu
820

<210> 153
<211> 820
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-69
<400> 153

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15
Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30
Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45
Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60
Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80
Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95
Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110
Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125
Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140
Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160
Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175
Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190
Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220
Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240
Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255
Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270
Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285
Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300
Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320
Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335
Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350
Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365
Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380
Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400
Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415
Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430
Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445
Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460
Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480
Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495
Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510
Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala

515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu

530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys

545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val

565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Gly Gly Gly Ser Gly Gly

580 585 590

Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe

595 600 605

Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln

610 615 620

Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys

625 630 635 640

Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His

645 650 655

Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg

660 665 670

Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys

675 680 685

Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr

690 695 700

Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met

705 710 715 720

Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val

725 730 735

Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu Gly Gly Gly Gly Ser

740 745 750

Gly Gly Gly Gly Ser Phe Val Asn Gln His Leu Cys Gly Ser His Leu

755 760 765

Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr

770 775 780

Pro Lys Thr Gly Ser Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr Gly

785 790 795 800

Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu

805 810 815

Asn Tyr Cys Asn

820

<210> 154
<211> 821
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-70
<400> 154

Met Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
1 5 10 15
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
20 25 30
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
35 40 45
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
50 55 60
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
65 70 75 80
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
85 90 95
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
100 105 110
Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
115 120 125
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
130 135 140
Thr Lys Phe Tyr Phe Gln Glu Asp Glu Gly Gly Gly Gly Ser Gly Gly
145 150 155 160
Gly Gly Ser Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp
165 170 175
Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln
180 185 190
Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu
195 200 205
Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn
210 215 220
Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val
225 230 235 240
Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys
245 250 255

Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn
260 265 270
Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr
275 280 285
Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu
290 295 300
Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe
305 310 315 320
Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp
325 330 335
Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly
340 345 350
Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys
355 360 365
Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln
370 375 380
Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp
385 390 395 400
Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys
405 410 415
Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp
420 425 430
Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu
435 440 445
Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp
450 455 460
Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys
465 470 475 480
Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu
485 490 495
Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu
500 505 510
Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp
515 520 525
Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val
530 535 540
Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln
545 550 555 560
Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys

565 570 575
Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn
580 585 590
Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg
595 600 605
Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys
610 615 620
Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys
625 630 635 640
Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val
645 650 655
Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe
660 665 670
His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys
675 680 685
Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys
690 695 700
Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys
705 710 715 720
Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys
725 730 735
Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Gly Gly Gly
740 745 750
Ser Gly Gly Gly Gly Ser Phe Val Asn Gln His Leu Cys Gly Ser His
755 760 765
Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr
770 775 780
Thr Pro Lys Thr Gly Ala Gly Ser Ser Ser Ala Ala Ala Pro Gln Thr
785 790 795 800
Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu
805 810 815
Glu Asn Tyr Cys Asn
820

<210> 155
<211> 199
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-1

<400> 155

Tyr Ser Glu Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Gly Lys
20 25 30
Lys Asn Asp Trp Lys His Asn Ile Thr Gln Gly Gly Gly Gly Ser Arg
35 40 45
Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp
50 55 60
Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly
65 70 75 80
Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val
85 90 95
Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met
100 105 110
Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu
115 120 125
Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg
130 135 140
Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser
145 150 155 160
Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln
165 170 175
Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys
180 185 190
Phe Tyr Phe Gln Glu Asp Glu
195

<210> 156

<211> 194

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 GI-2

<400> 156

Tyr Ala Glu Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Gly Lys
20 25 30
Lys Asn Asp Trp Lys His Asn Ile Thr Gln Arg Pro Ser Gly Arg Lys

35 40 45

Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr
50 55 60

Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro
65 70 75 80

Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His
85 90 95

Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val
100 105 110

Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr
115 120 125

Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg
130 135 140

Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly
145 150 155 160

Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr
165 170 175

Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu
180 185 190

Asp Glu

<210> 157

<211> 199

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 GI-3

<400> 157

Tyr Ala Glu Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15

Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Gly Lys
20 25 30

Lys Asn Asp Trp Lys His Asn Ile Thr Gln Gly Gly Gly Gly Ser Arg
35 40 45

Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp
50 55 60

Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly
65 70 75 80

Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val
85 90 95

Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met
100 105 110
Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu
115 120 125
Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg
130 135 140
Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser
145 150 155 160
Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln
165 170 175
Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys
180 185 190
Phe Tyr Phe Gln Glu Asp Glu
195

<210> 158
<211> 204
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-4
<400> 158
Tyr Ala Glu Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Gly Lys
20 25 30
Lys Asn Asp Trp Lys His Asn Ile Thr Gln Gly Gly Gly Gly Ser Gly
35 40 45
Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala
50 55 60
Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn
65 70 75 80
Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu
85 90 95
Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile
100 105 110
His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr
115 120 125
Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg
130 135 140

Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr
145 150 155 160
Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala
165 170 175
Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly
180 185 190
Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 159
<211> 209
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-5
<400> 159
Tyr Ala Glu Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Gly Lys
20 25 30
Lys Asn Asp Trp Lys His Asn Ile Thr Gln Gly Gly Gly Gly Ser Gly
35 40 45
Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser
50 55 60
Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe
65 70 75 80
Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn
85 90 95
Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala
100 105 110
Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys
115 120 125
Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp
130 135 140
Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser
145 150 155 160
Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp
165 170 175
Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn
180 185 190

Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp
195 200 205
Glu
<210> 160
<211> 194
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-6
<400> 160
Tyr Ala Pro Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Gly Lys
20 25 30
Lys Asn Asp Trp Lys His Asn Ile Thr Gln Arg Pro Ser Gly Arg Lys
35 40 45
Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr
50 55 60
Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro
65 70 75 80
Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His
85 90 95
Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val
100 105 110
Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr
115 120 125
Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg
130 135 140
Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly
145 150 155 160
Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr
165 170 175
Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu
180 185 190
Asp Glu
<210> 161
<211> 199
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白 GI-7
<400> 161
Tyr Ala Pro Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Gly Lys
20 25 30
Lys Asn Asp Trp Lys His Asn Ile Thr Gln Gly Gly Gly Gly Ser Arg
35 40 45
Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp
50 55 60
Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly
65 70 75 80
Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val
85 90 95
Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met
100 105 110
Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu
115 120 125
Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg
130 135 140
Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser
145 150 155 160
Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln
165 170 175
Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys
180 185 190
Phe Tyr Phe Gln Glu Asp Glu
195
<210> 162
<211> 204
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-8
<400> 162
Tyr Ala Pro Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Gly Lys

20 25 30
Lys Asn Asp Trp Lys His Asn Ile Thr Gln Gly Gly Gly Gly Ser Gly
35 40 45
Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala
50 55 60
Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn
65 70 75 80
Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu
85 90 95
Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile
100 105 110
His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr
115 120 125
Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg
130 135 140
Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr
145 150 155 160
Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala
165 170 175
Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly
180 185 190
Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 163
<211> 209
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-9
<400> 163
Tyr Ala Pro Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Gly Lys
20 25 30
Lys Asn Asp Trp Lys His Asn Ile Thr Gln Gly Gly Gly Gly Ser Gly
35 40 45
Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser
50 55 60
Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe

65 70 75 80
Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn
85 90 95
Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala
100 105 110
Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys
115 120 125
Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp
130 135 140
Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser
145 150 155 160
Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp
165 170 175
Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn
180 185 190
Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp
195 200 205
Glu

<210> 164
<211> 195
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 IN-10
<400> 164
Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys Ile His Gln Gln Asp Phe
1 5 10 15
Val Asn Trp Leu Leu Ala Gln Lys Pro Ser Ser Gly Ala Pro Pro Pro
20 25 30
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg
35 40 45
Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys
50 55 60
Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly
65 70 75 80
Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro
85 90 95
His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys
100 105 110

Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile
115 120 125
Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile
130 135 140
Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro
145 150 155 160
Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu
165 170 175
Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln
180 185 190
Glu Asp Glu
195

<210> 165
<211> 206
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-11
<400> 165

Tyr Gly Glu Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met
50 55 60
Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg
65 70 75 80
Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu
85 90 95
Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu
100 105 110
Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp
115 120 125
Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu
130 135 140
Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly
145 150 155 160

Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys
165 170 175
Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp
180 185 190
Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200 205

<210> 166
<211> 196
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-12
<400> 166

Tyr Gly Glu Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly
35 40 45
Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln
50 55 60
Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln
65 70 75 80
Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu
85 90 95
Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser
100 105 110
Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn
115 120 125
Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe
130 135 140
Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys
145 150 155 160
Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser
165 170 175
Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe
180 185 190
Gln Glu Asp Glu
195

<210> 167
<211> 206
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-13
<400> 167

```
Tyr Ala Glu Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1               5                  10                  15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Pro Ser
            20                  25                  30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        35                  40                  45
Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met
    50                  55                  60
Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg
65                  70                  75                  80
Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu
                85                  90                  95
Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu
            100                 105                 110
Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp
        115                 120                 125
Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu
    130                 135                 140
Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly
145                 150                 155                 160
Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys
                165                 170                 175
Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp
            180                 185                 190
Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
        195                 200                 205
```

<210> 168
<211> 201
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-14

<400> 168

Tyr Ala Glu Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
50 55 60
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
85 90 95
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
100 105 110
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
115 120 125
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
130 135 140
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
145 150 155 160
Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
165 170 175
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
180 185 190
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 169

<211> 196

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 GI-15

<400> 169

Tyr Ala Glu Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly

35 40 45

Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln
50 55 60

Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln
65 70 75 80

Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu
85 90 95

Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser
100 105 110

Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn
115 120 125

Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe
130 135 140

Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys
145 150 155 160

Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser
165 170 175

Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe
180 185 190

Gln Glu Asp Glu
195

<210> 170
<211> 187
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-16
<400> 170

Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys Ile His Gln Gln Asp
1 5 10 15

Phe Val Asn Trp Leu Leu Ala Gln Lys Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe
35 40 45

Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln
50 55 60

Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys
65 70 75 80

Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His

85 90 95
Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg
100 105 110
Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys
115 120 125
Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr
130 135 140
Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met
145 150 155 160
Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val
165 170 175
Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
180 185

<210> 171
<211> 182
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-17
<400> 171
Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys Ile His Gln Gln Asp
1 5 10 15
Phe Val Asn Trp Leu Leu Ala Gln Lys Gly Gly Gly Gly Ser Arg Pro
20 25 30
Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val
35 40 45
Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr
50 55 60
Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro
65 70 75 80
Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys
85 90 95
Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala
100 105 110
Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe
115 120 125
Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala
130 135 140
Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro

145 150 155 160
Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe
165 170 175
Tyr Phe Gln Glu Asp Glu
180
<210> 172
<211> 196
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-18
<400> 172
Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys Ile His Gln Gln Asp
1 5 10 15
Phe Val Asn Trp Leu Leu Ala Gln Lys Pro Ser Ser Gly Ala Pro Pro
20 25 30
Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly
35 40 45
Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln
50 55 60
Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln
65 70 75 80
Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu
85 90 95
Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser
100 105 110
Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn
115 120 125
Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe
130 135 140
Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys
145 150 155 160
Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser
165 170 175
Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe
180 185 190
Gln Glu Asp Glu
195
<210> 173

<211> 182
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-19
<400> 173

Tyr Ala Pro Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Arg Pro
20 25 30
Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val
35 40 45
Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr
50 55 60
Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro
65 70 75 80
Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys
85 90 95
Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala
100 105 110
Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe
115 120 125
Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala
130 135 140
Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro
145 150 155 160
Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe
165 170 175
Tyr Phe Gln Glu Asp Glu
180

<210> 174
<211> 196
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-20
<400> 174

Tyr Ala Pro Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15

Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Arg Pro Ser Gly
35 40 45
Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln
50 55 60
Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln
65 70 75 80
Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu
85 90 95
Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser
100 105 110
Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn
115 120 125
Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe
130 135 140
Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys
145 150 155 160
Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser
165 170 175
Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe
180 185 190
Gln Glu Asp Glu
195

<210> 175
<211> 201
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-21
<400> 175
Tyr Ala Pro Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
35 40 45
Ser Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
50 55 60

Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
65 70 75 80
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
85 90 95
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
100 105 110
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
115 120 125
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
130 135 140
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
145 150 155 160
Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
165 170 175
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
180 185 190
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
195 200

<210> 176
<211> 789
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-22
<400> 176
Tyr Ala Glu Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Gly Lys
20 25 30
Lys Asn Asp Trp Lys His Asn Ile Thr Gln Gly Gly Gly Gly Ser Arg
35 40 45
Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp
50 55 60
Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly
65 70 75 80
Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val
85 90 95
Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met
100 105 110

Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu
115 120 125
Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg
130 135 140
Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser
145 150 155 160
Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln
165 170 175
Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys
180 185 190
Phe Tyr Phe Gln Glu Asp Glu Gly Gly Gly Gly Ser Asp Ala His Lys
195 200 205
Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
210 215 220
Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe
225 230 235 240
Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
245 250 255
Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
260 265 270
Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
275 280 285
Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
290 295 300
Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
305 310 315 320
Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
325 330 335
Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr
340 345 350
Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala
355 360 365
Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro
370 375 380
Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
385 390 395 400
Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
405 410 415
Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe

420 425 430

Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu

435 440 445

Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu

450 455 460

Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys

465 470 475 480

Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu

485 490 495

Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp

500 505 510

Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp

515 520 525

Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp

530 535 540

Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr

545 550 555 560

Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys

565 570 575

Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile

580 585 590

Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln

595 600 605

Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr

610 615 620

Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys

625 630 635 640

Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr

645 650 655

Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro

660 665 670

Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg

675 680 685

Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys

690 695 700

Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu

705 710 715 720

Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu

725 730 735

Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
740 745 750
Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
755 760 765
Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
770 775 780
Ala Ala Leu Gly Leu
785

<210> 177
<211> 789
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-23
<400> 177

Tyr Ala Pro Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Gly Lys
20 25 30
Lys Asn Asp Trp Lys His Asn Ile Thr Gln Gly Gly Gly Gly Ser Arg
35 40 45
Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp
50 55 60
Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly
65 70 75 80
Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val
85 90 95
Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met
100 105 110
Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu
115 120 125
Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg
130 135 140
Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser
145 150 155 160
Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln
165 170 175
Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr Lys
180 185 190

Phe Tyr Phe Gln Glu Asp Glu Gly Gly Gly Gly Ser Asp Ala His Lys
195 200 205
Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
210 215 220
Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe
225 230 235 240
Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
245 250 255
Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
260 265 270
Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
275 280 285
Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
290 295 300
Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
305 310 315 320
Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
325 330 335
Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr
340 345 350
Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala
355 360 365
Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro
370 375 380
Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
385 390 395 400
Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
405 410 415
Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe
420 425 430
Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu
435 440 445
Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu
450 455 460
Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys
465 470 475 480
Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu
485 490 495
Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp

500 505 510

Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp
515 520 525

Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp
530 535 540

Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr
545 550 555 560

Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys
565 570 575

Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile
580 585 590

Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln
595 600 605

Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr
610 615 620

Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys
625 630 635 640

Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr
645 650 655

Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro
660 665 670

Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg
675 680 685

Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys
690 695 700

Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu
705 710 715 720

Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu
725 730 735

Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
740 745 750

Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
755 760 765

Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
770 775 780

Ala Ala Leu Gly Leu
785

<210> 178

<211> 153

<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-24
<220>
<221> MOD_RES
<222> (85)..(85)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GIP受体结合多肽,S是半胱氨酸侧链的硫原子,其中GIP受体结合多肽的序列是SEQ ID NO:197
<400> 178

```
Met Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
1               5                  10                  15
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
            20                  25                  30
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
        35                  40                  45
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
    50                  55                  60
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
65                  70                  75                  80
Leu Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
                85                  90                  95
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
            100                 105                 110
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
        115                 120                 125
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
    130                 135                 140
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
145                 150
```

<210> 179
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-25
<220>
<221> MOD_RES
<222> (116)..(116)

<223> S -马来酰亚胺-PEG40K
-马来酰亚胺-S-GIP受体结合多肽,S是半胱氨酸侧链的硫原子,GIP受体结合多肽的序列是SEQ ID NO:198
<400> 179

Arg	Pro	Ser	Gly	Arg	Lys	Ser	Ser	Lys	Met	Gln	Ala	Phe	Arg	Ile	Trp
1				5				10					15		
Asp	Val	Asn	Gln	Lys	Thr	Phe	Tyr	Leu	Arg	Asn	Asn	Gln	Leu	Val	Ala
			20					25				30			
Gly	Tyr	Leu	Gln	Gly	Pro	Asn	Val	Asn	Leu	Glu	Glu	Lys	Ile	Asp	Val
		35					40					45			
Val	Pro	Ile	Glu	Pro	His	Ala	Leu	Phe	Leu	Gly	Ile	His	Gly	Gly	Lys
	50					55					60				
Met	Cys	Leu	Ser	Cys	Val	Lys	Ser	Gly	Asp	Glu	Thr	Arg	Leu	Gln	Leu
65					70					75					80
Glu	Ala	Val	Asn	Ile	Thr	Asp	Leu	Ser	Glu	Asn	Arg	Lys	Gln	Asp	Lys
				85					90					95	
Arg	Phe	Ala	Phe	Ile	Arg	Ser	Asp	Ser	Gly	Pro	Thr	Thr	Ser	Phe	Glu
			100					105					110		
Ser	Ala	Ala	Cys	Pro	Gly	Trp	Phe	Leu	Cys	Thr	Ala	Met	Glu	Ala	Asp
		115					120					125			
Gln	Pro	Val	Ser	Leu	Thr	Asn	Met	Pro	Asp	Glu	Gly	Val	Met	Val	Thr
	130					135					140				
Lys	Phe	Tyr	Phe	Gln	Glu	Asp	Glu								
145					150										

<210> 180
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-26
<220>
<221> MOD_RES
<222> (116)..(116)
<223> S -马来酰亚胺-PEG40K
-马来酰亚胺-S-GIP受体结合多肽,S是半胱氨酸侧链的硫原子,其中GIP受体结合多肽的序列是SEQ ID NO:199
<400> 180

Arg	Pro	Ser	Gly	Arg	Lys	Ser	Ser	Lys	Met	Gln	Ala	Phe	Arg	Ile	Trp
1				5				10					15		

Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 181
<211> 154
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-27
<220>
<221> MOD_RES
<222> (154)..(154)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GIP受体结合多肽,S是半胱氨酸侧链的硫原子,其中GIP受体结合多肽的序列是SEQ ID NO:200
<400> 181
Met Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
1 5 10 15
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
20 25 30
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
35 40 45
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
50 55 60
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln

65 70 75 80
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
85 90 95
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
100 105 110
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
115 120 125
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
130 135 140
Thr Lys Phe Tyr Phe Gln Glu Asp Glu Cys
145 150

<210> 182
<211> 153
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-28
<220>
<221> MOD_RES
<222> (1)..(1)
<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GIP受体结合多肽,S是半胱氨酸侧链的硫原子,GIP受体结合多肽的序列是SEQ ID NO:201
<220>
<221> MOD_RES
<222> (117)..(117)
<223> S-CH2-CONH-(CH2CH2O)4-(CH2)2-NH-(Nα-(HOOC(CH2)16CO)-γ-Glu)
<400> 182
Cys Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
1 5 10 15
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
20 25 30
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
35 40 45
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
50 55 60
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
65 70 75 80
Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
85 90 95

Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
100 105 110
Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
115 120 125
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
130 135 140
Thr Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 183
<211> 153
<212> PRT
<213> 人工序列
<220>
<223> 融合蛋白 GI-29
<220>
<221> MOD_RES
<222> (85)..(85)
<223> S-马来酰亚胺-PEG40K-马来酰亚胺-S-GIP受体结合多肽,S是半胱氨酸侧链的硫原子,其中GIP受体结合多肽的序列是SEQ ID NO:202
<400> 183
Met Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
1 5 10 15
Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
20 25 30
Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
35 40 45
Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
50 55 60
Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
65 70 75 80
Leu Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
85 90 95
Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
100 105 110
Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
115 120 125
Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val
130 135 140
Thr Lys Phe Tyr Phe Gln Glu Asp Glu

145 150

<210> 184

<211> 152

<212> PRT

<213> 人工序列

<220>

<223> 融合蛋白 GI-30

<220>

<221> MOD_RES

<222> (116)..(116)

<223> S-马来酰亚胺-PEG11-马来酰亚胺-S-GIP受体结合多肽,S是半胱氨酸侧链的硫原子,其中GIP受体结合多肽的序列是SEQ ID NO:203

<400> 184

Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 185

<211> 39

<212> PRT

<213> 人工序列

<220>

<223> GLP-1受体结合多肽

<400> 185
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Cys
35
<210> 186
<211> 31
<212> PRT
<213> 人工序列
<220>
<223> GLP-1受体结合多肽
<400> 186
His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Cys
20 25 30
<210> 187
<211> 31
<212> PRT
<213> 人工序列
<220>
<223> GLP-1受体结合多肽
<400> 187
His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Cys Gly Arg Gly
20 25 30
<210> 188
<211> 39
<212> PRT
<213> 人工序列
<220>
<223> GLP-1受体结合多肽
<400> 188
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Cys Asn Gly Gly Pro Ser

20 25 30

Ser Gly Ala Pro Pro Pro Ser

35

<210> 189

<211> 31

<212> PRT

<213> 人工序列

<220>

<223> GLP-1受体结合多肽

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> 2-甲基丙氨酸

<400> 189

His Xaa Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly

1 5 10 15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Cys

20 25 30

<210> 190

<211> 31

<212> PRT

<213> 人工序列

<220>

<223> GLP-1受体结合多肽

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> 2-甲基丙氨酸

<400> 190

His Xaa Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly

1 5 10 15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Cys Gly Arg Gly

20 25 30

<210> 191

<211> 31

<212> PRT

<213> 人工序列

<220>

<223> GLP-1受体结合多肽

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> 2-甲基丙氨酸
<400> 191
His Xaa Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Cys
20 25 30
<210> 192
<211> 31
<212> PRT
<213> 人工序列
<220>
<223> GLP-1受体结合多肽
<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> 2-甲基丙氨酸
<400> 192
His Xaa Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
1 5 10 15
Gln Ala Ala Cys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly
20 25 30
<210> 193
<211> 31
<212> PRT
<213> 人工序列
<220>
<223> GLP-1受体结合多肽
<220>
<221> MOD_RES
<222> (20)..(20)
<223> Nε-(Nα-(HOOC(CH2)14CO)-γ-L-Glu)
<400> 193
His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
1 5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Cys
20 25 30

<210> 194
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> IL-1ra
<400> 194

Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
35 40 45
Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60
Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80
Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95
Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110
Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125
Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140
Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 195
<211> 152
<212> PRT
<213> 人工序列
<220>
<223> 白介素-1受体拮抗蛋白
<400> 195

Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15
Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
20 25 30
Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val

35 40 45

Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
50 55 60

Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80

Glu Ala Val Cys Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
85 90 95

Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
100 105 110

Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
115 120 125

Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
130 135 140

Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 196
<211> 153
<212> PRT
<213> 人工序列
<220>
<223> IL-1ra
<400> 196

Cys Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile
1 5 10 15

Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val
20 25 30

Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp
35 40 45

Val Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly
50 55 60

Lys Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln
65 70 75 80

Leu Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp
85 90 95

Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe
100 105 110

Glu Ser Ala Ala Ser Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala
115 120 125

Asp Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val

130 135 140

Thr Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> 197
<211> 42
<212> PRT
<213> 人工序列
<220>
<223> GIP受体结合多肽
<400> 197

Tyr Ala Glu Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Gly Lys
20 25 30
Lys Asn Asp Trp Cys His Asn Ile Thr Gln
35 40

<210> 198
<211> 43
<212> PRT
<213> 人工序列
<220>
<223> GIP受体结合多肽
<400> 198

Tyr Ala Glu Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Gly Lys
20 25 30
Lys Asn Asp Trp Lys His Asn Ile Thr Gln Cys
35 40

<210> 199
<211> 43
<212> PRT
<213> 人工序列
<220>
<223> GIP受体结合多肽
<400> 199

Tyr Ala Pro Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Gly Lys

20 25 30

Lys Asn Asp Trp Lys His Asn Ile Thr Gln Cys

35 40

<210> 200

<211> 30

<212> PRT

<213> 人工序列

<220>

<223> GIP受体结合多肽

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> 2-甲基丙氨酸

<400> 200

Tyr Xaa Glu Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys

1 5 10 15

Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Cys

20 25 30

<210> 201

<211> 40

<212> PRT

<213> 人工序列

<220>

<223> GIP受体结合多肽

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> 2-甲基丙氨酸

<400> 201

Tyr Xaa Glu Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys

1 5 10 15

Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Pro Ser

20 25 30

Ser Gly Ala Pro Pro Pro Ser Cys

35 40

<210> 202

<211> 39

<212> PRT

<213> 人工序列

<220>
<223> GIP受体结合多肽
<400> 202
Tyr Ala Glu Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1 5 10 15
Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Cys
35
<210> 203
<211> 26
<212> PRT
<213> 人工序列
<220>
<223> GIP受体结合多肽
<400> 203
Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys Ile His Gln Gln Asp
1 5 10 15
Phe Val Asn Trp Leu Leu Ala Gln Lys Cys
20 25

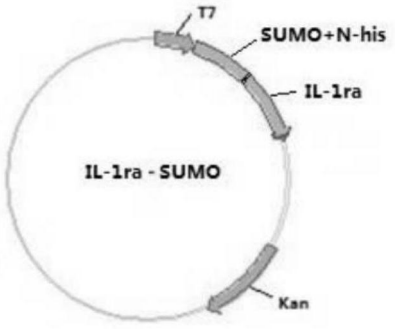

T7
SUMO+N-his
IL-1ra
IL-1ra-SUMO
Kan

图1A

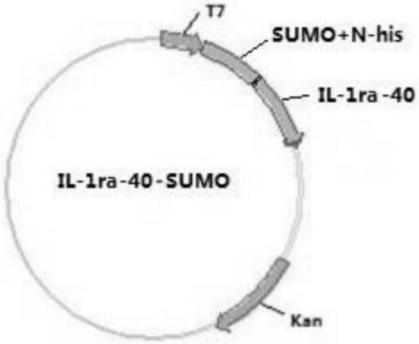

T7
SUMO+N-his
IL-1ra-40
IL-1ra-40-SUMO
Kan

图1B


Nucleotides sequence alignment:
Clone Manager
View Clone Map Primer Align Discover Operations Window Help
IL-1ra-full (579bps)
IL-1ra-SEQ (1091bps)
IL-1ra-40-SEQ (1111bps)
IL-1ra-40 (459bps)
Align Multi 1
Global DNA alignment. Reference molecule: IL-1ra-full, Region 1 to 579
Sequences: 4. Scoring matrix: Linear (Mismatch 2, OpenGap 4, ExtGap 1)
Sequence View: Similarity Format, Color areas of high matches at same base position
IL-1ra-full
IL-1ra-SEQ
IL-1ra-40
IL-1ra-40-SE
Info
Sequence
LMap

图2

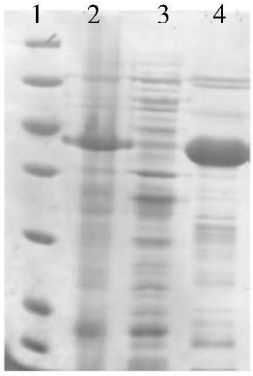

1
2
3
4

图3A

图3B

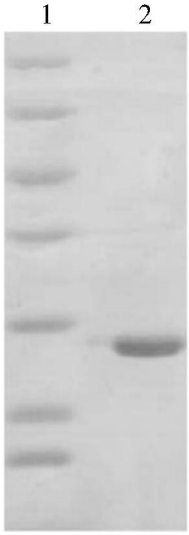


图3C

RP-HPLC ：

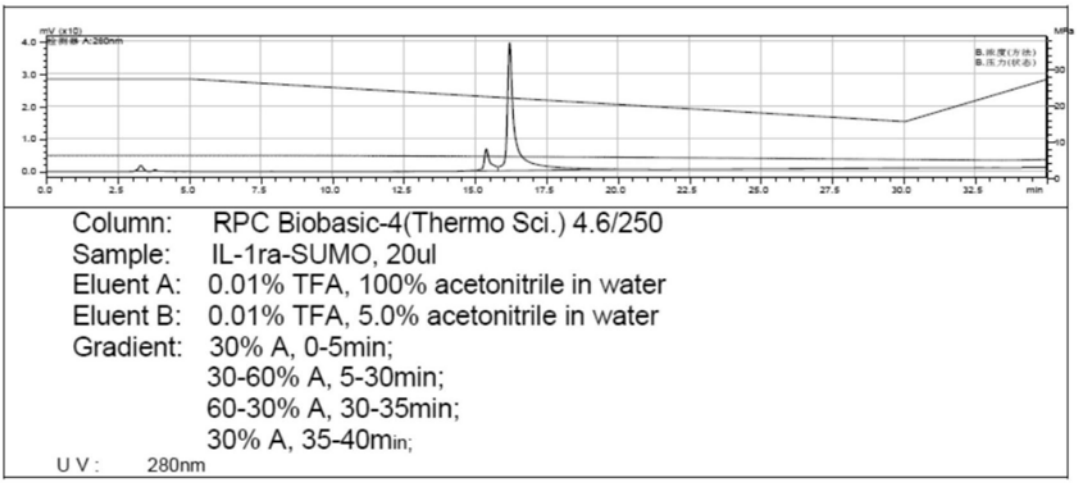

Column: RPC Biobasic-4(Thermo Sci.) 4.6/250
Sample: IL-1ra-SUMO, 20ul
Eluent A: 0.01% TFA, 100% acetonitrile in water
Eluent B: 0.01% TFA, 5.0% acetonitrile in water
Gradient: 30% A, 0-5min;
30-60% A, 5-30min;
60-30% A, 30-35min;
30% A, 35-40min;
U V : 280nm

图4

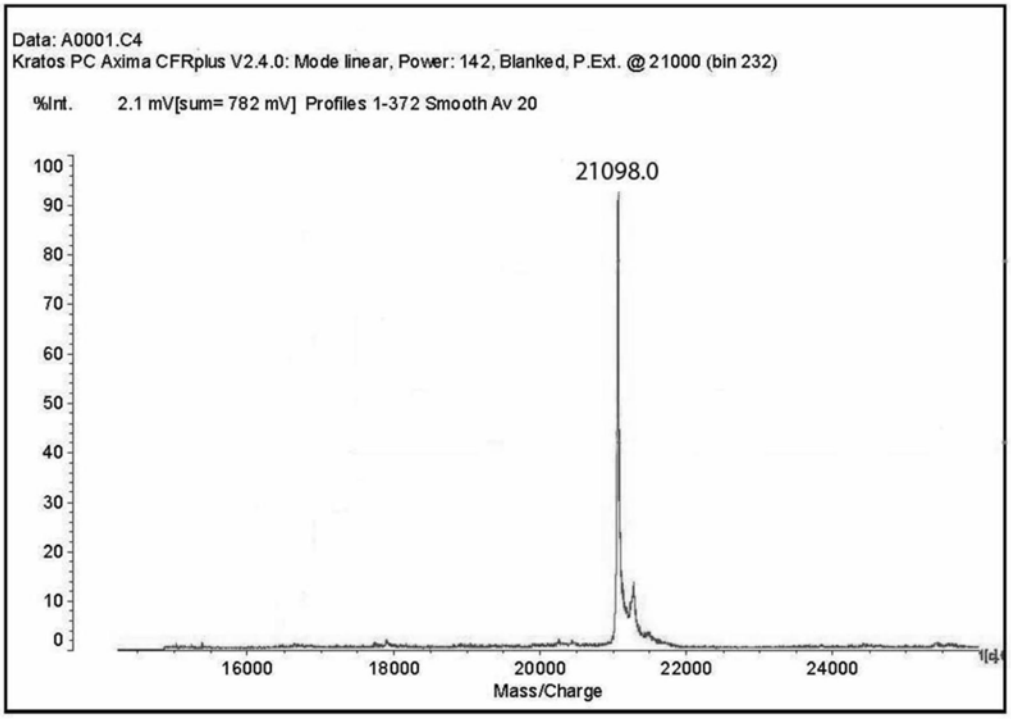
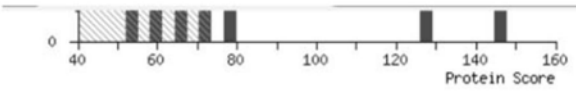

Data: A0001.C4
Kratos PC Axima CFRplus V2.4.0: Mode linear, Power: 142, Blanked, P.Ext. @ 21000 (bin 232)
%Int. 2.1 mV[sum= 782 mV] Profiles 1-372 Smooth Av 20
21098.0
100
90
80
70
60
50
40
30
20
10
0
16000
18000
20000
22000
24000
Mass/Charge

图5



Concise Protein Summary Report

Format As | Concise Protein Summary | Help

Significance threshold p< 0.05 | Max. number of hits 5

Re-Search All | Search Unmatched

1. gi|27894321 **Mass:** 16360 **Score:** 146 **Expect:** 2.8e-09 **Matches:** 12
interleukin-1 receptor antagonist protein isoform 4 [Homo sapiens]
gi|114579657 **Mass:** 16390 **Score:** 146 **Expect:** 2.8e-09 **Matches:** 12
PREDICTED: interleukin-1 receptor antagonist protein isoform 2 [Pan troglodytes]
gi|640248 **Mass:** 17344 **Score:** 132 **Expect:** 7.1e-08 **Matches:** 12
Chain A, Initial Crystallographic Analyses Of A Recombinant Interleukin-1 Receptor Antagonist Protein
gi|157831496 **Mass:** 17475 **Score:** 129 **Expect:** 1.4e-07 **Matches:** 12
Chain A, Solution Structure Of Human Interleukin-1 Receptor Antagonist Protein
gi|10835147 **Mass:** 18162 **Score:** 128 **Expect:** 1.8e-07 **Matches:** 12
interleukin-1 receptor antagonist protein isoform 3 [Homo sapiens]
gi|55600494 **Mass:** 18178 **Score:** 128 **Expect:** 1.8e-07 **Matches:** 12
PREDICTED: interleukin-1 receptor antagonist protein isoform 4 [Pan troglodytes]
gi|27894317 **Mass:** 20170 **Score:** 125 **Expect:** 3.6e-07 **Matches:** 12

图6A

Protein sequence coverage: 55%

Matched peptides shown in ***bold red***.

```
  1 RPSGRKSSKM QAFRIWDVNQ KTFYLRNNQL VAGYLQGPNV NLEEKIDVVP
 51 IEPHALFLGI HGGKMCLSCV KSGDETRLQL EAVNITDLSE NRKQDKRFAF
101 IRSDSGPTTS FESAACPGWF LCTAMEADQP VSLTNMPDEG VMVTKFYFQE
151 DE
```

Unformatted sequence string: 152 residues (for pasting into other applications).

Sort peptides by ◉ Residue Number ○ Increasing Mass ○ Decreasing Mass

Show predicted peptides also

Start - End	Observed	Mr(expt)	Mr(calc)	Delta	M	Peptide
10 - 21	1535.7800	1534.7727	1534.7715	0.0013	1	K.MQAFRIWDVNQK.T
10 - 21	1551.7900	1550.7827	1550.7664	0.0164	1	K.MQAFRIWDVNQK.T + Oxidation (M)

图6B

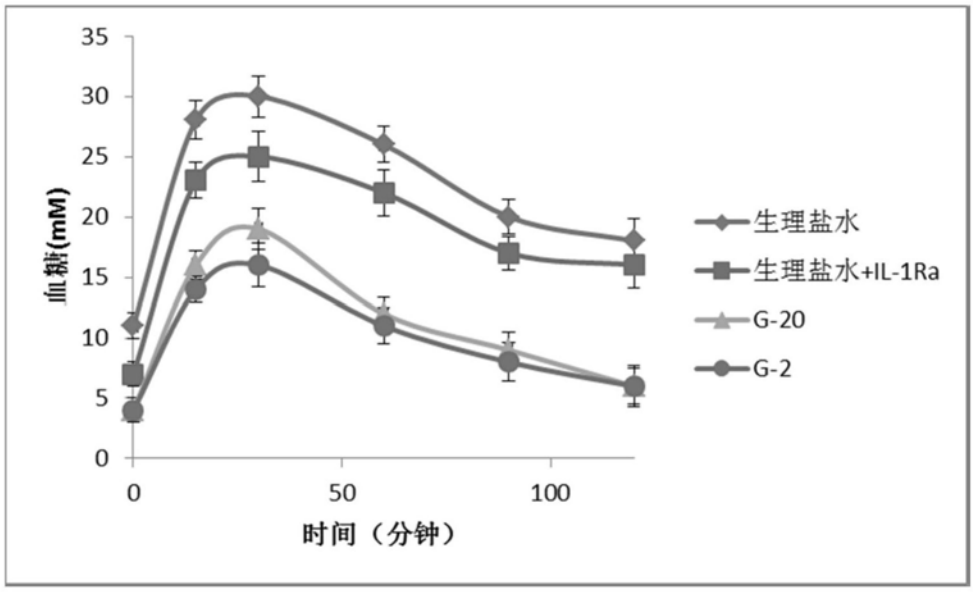

35
30
25
20
15
10
5
0
血糖(mM)
0
50
100
时间（分钟）
生理盐水
生理盐水+IL-1Ra
G-20
G-2

图7

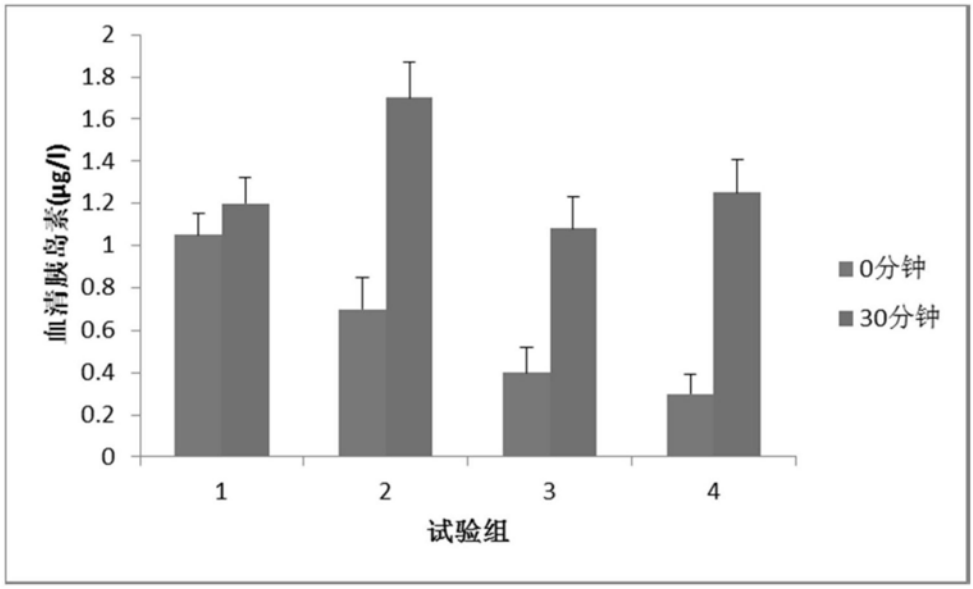

2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
血清胰岛素(μg/l)
1
2
3
4
试验组
0分钟
30分钟

图8

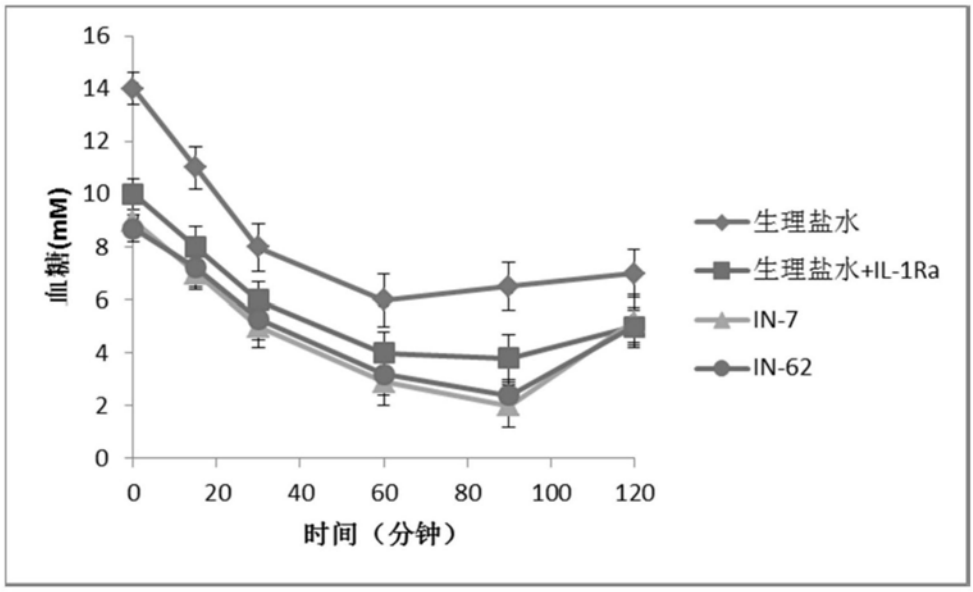

血糖(mM)
时间（分钟）
生理盐水
生理盐水+IL-1Ra
IN-7
IN-62

图9

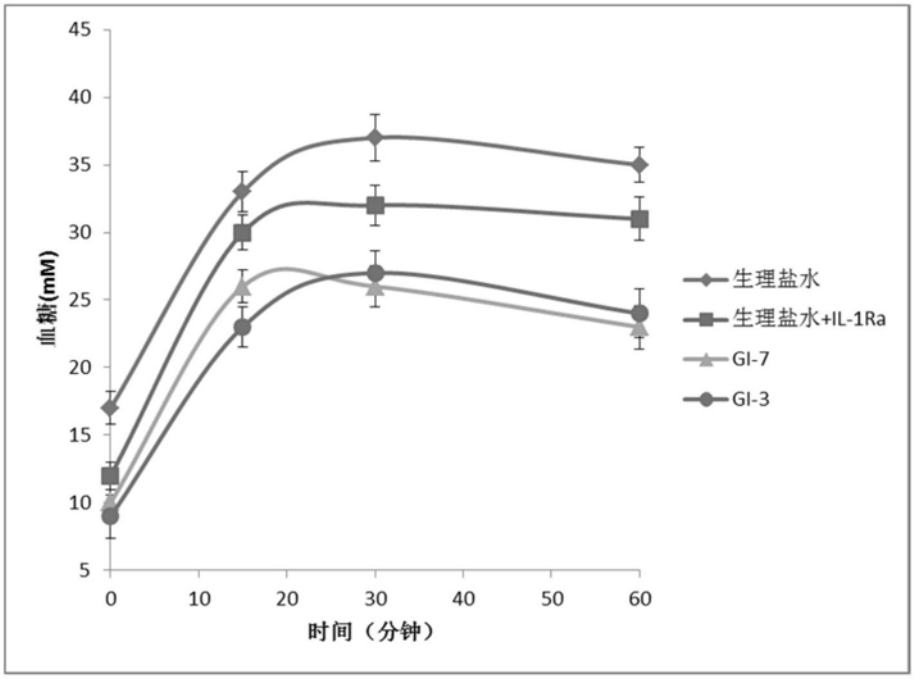

血糖(mM)
时间（分钟）
生理盐水
生理盐水+IL-1Ra
GI-7
GI-3

图10